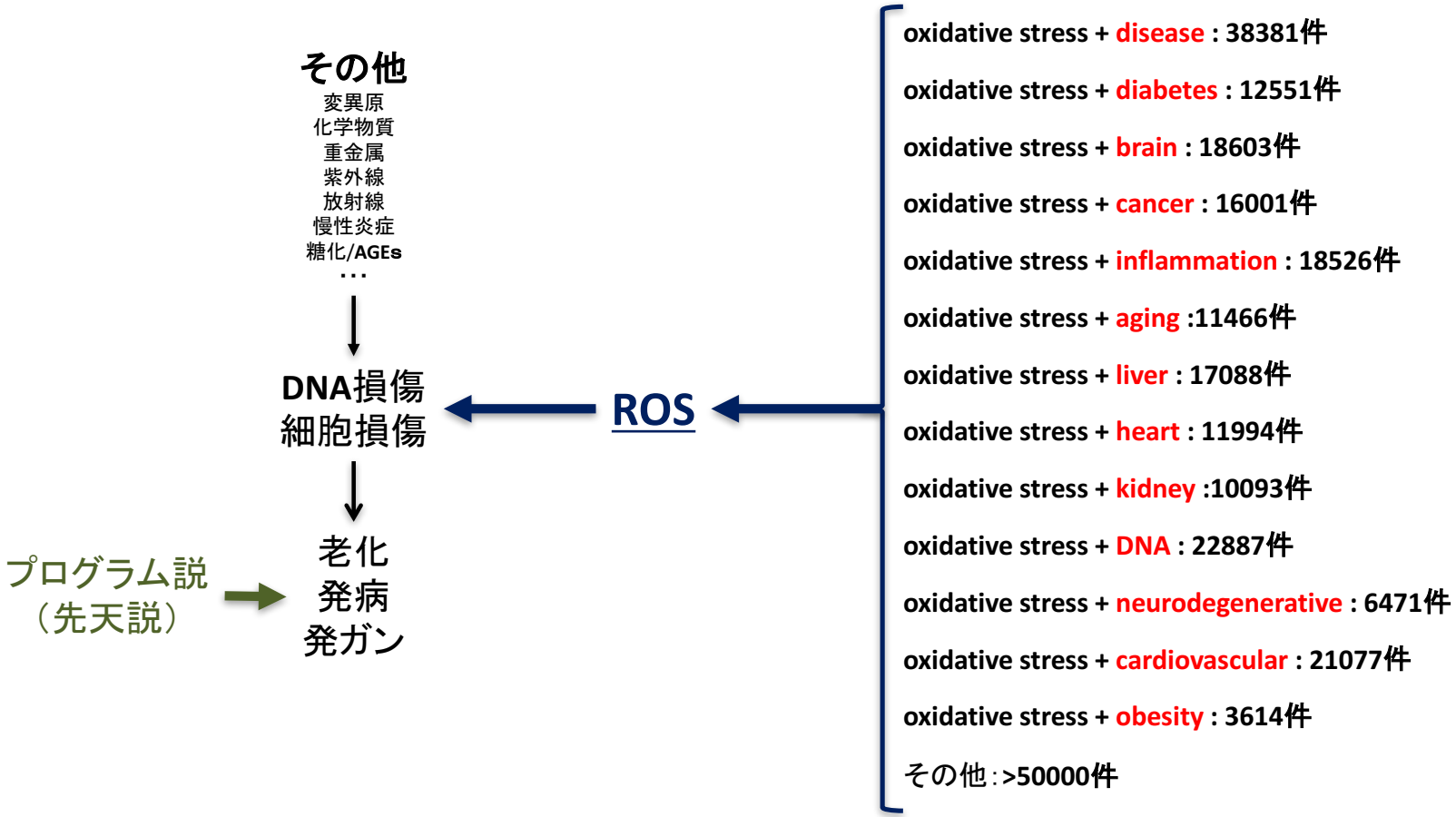
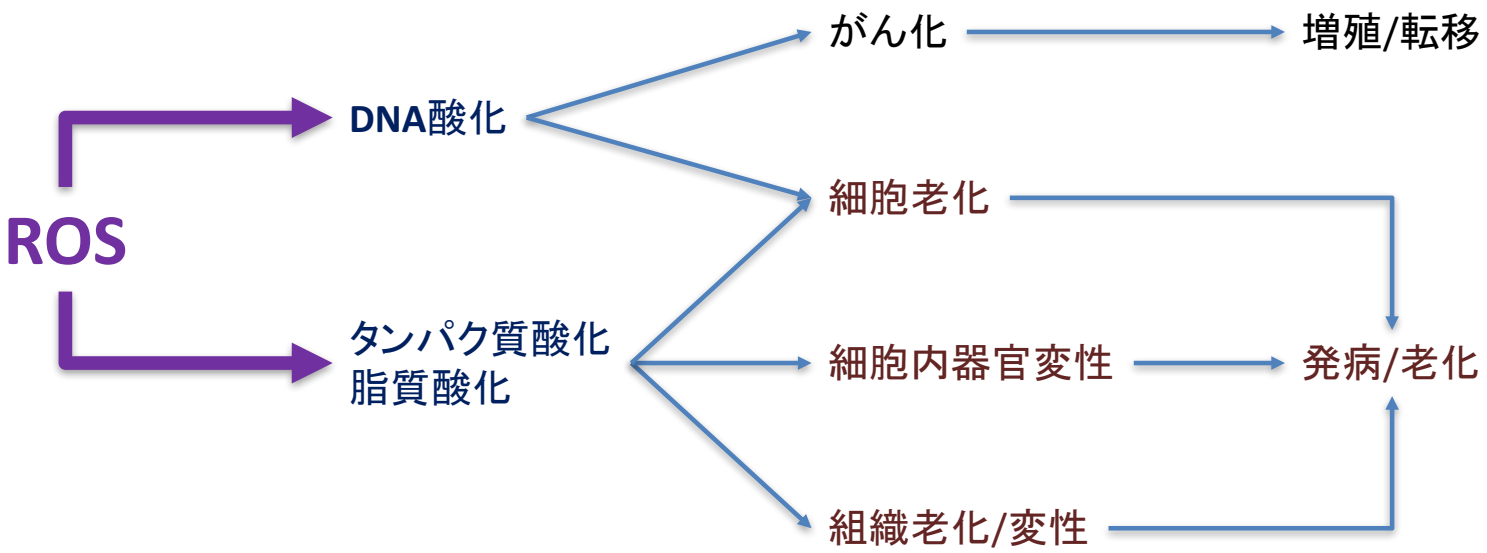
臨床水素治療研究会セミナー

Tsuji Naoki MD.

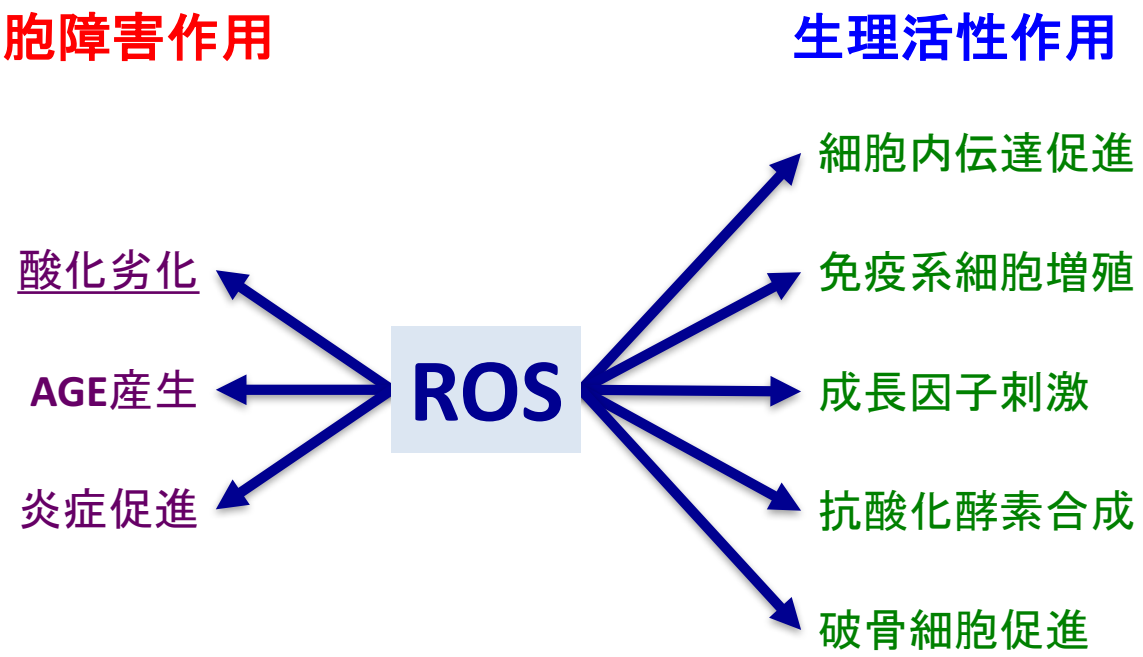
酸化ストレスと老化/慢性疾患の研究



活性酸素とがん化/老化/発病



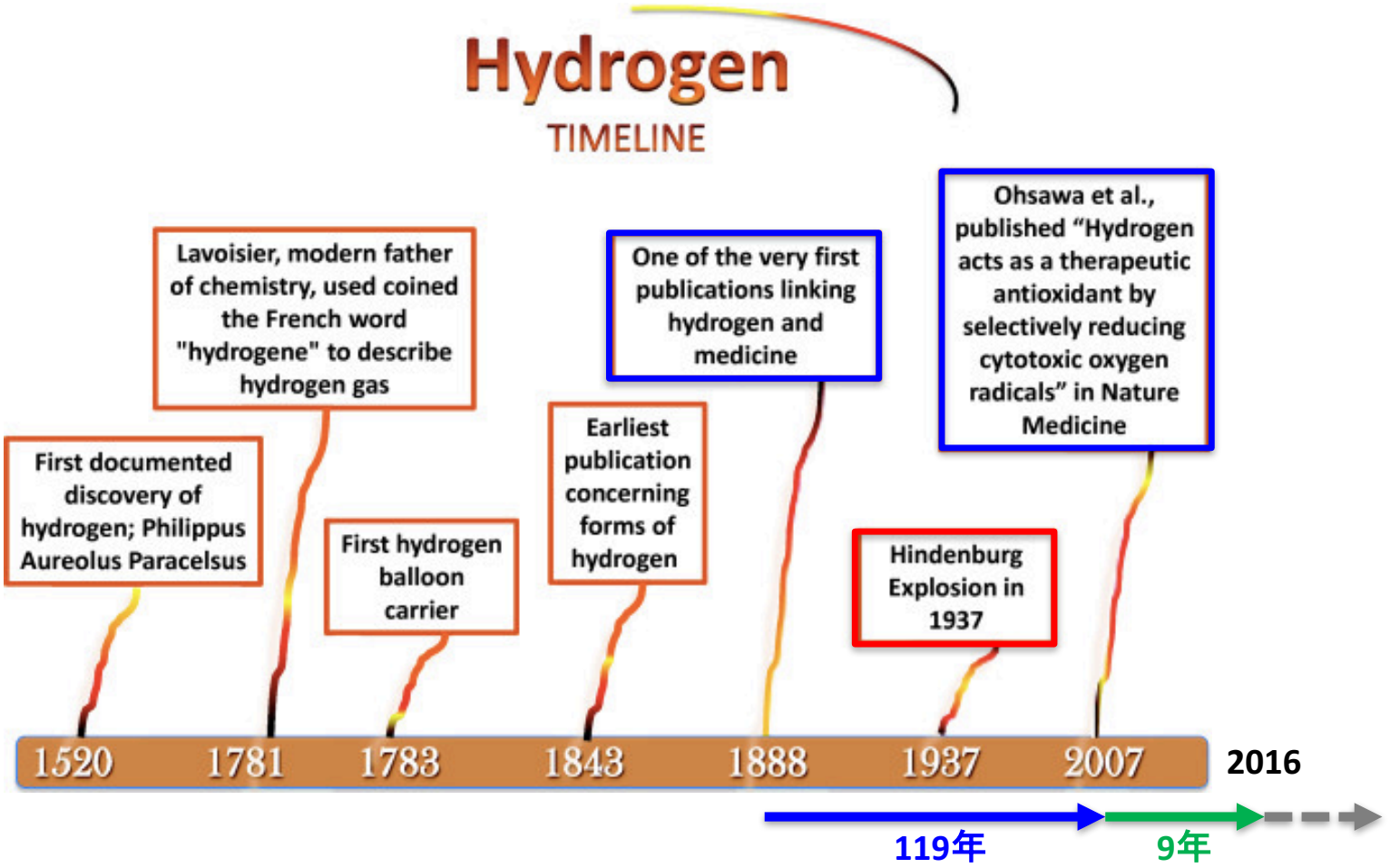
ROS：二つの顔



善か悪か？

水素医学の歴史

水素と水素の医学利用の歴史



1888：水素に関する初の医学論文

EDITORIAL ARTICLES.

SENN ON THE DIAGNOSIS OF GASTRO-INTESTINAL PERFORATION BY THE RECTAL INSUFFLATION OF HYDROGEN GAS.

The fertile mind of Professor Senn is notable for the originality of its conceptions. Our readers have been favored during the last half year with an account of his remarkable work in the treatment of intestinal obstruction, as presented to the Ninth International Medical Congress a year ago. Dr. Senn has not been satisfied to rest content with the laurels won by his previous labors in abdominal surgery, but has continued his vivisection experiments into the diagnosis of intestinal perforation.[1]

The fact that intestinal perforation can be treated by suture with success is now fully established. And it may also be considered as demonstrated that a traumatic perforation of any portion of the gastro-intestinal canal is inevitably fatal unless it be treated by suture.

The fact that a small number of cases are on record in which undoubted perforation of the gut recovered without other than expectant treatment can not be regarded as militating against the truth of this general rule, since they form so small a portion of the total that they may be ignored in the consideration of the subject.

In opposition to this condition may be placed simple perforating wounds of the abdominal parietes without lesion of the viscera, a condition amenable to simple closure of the external wound and comparatively innocuous.

But the great difficulty that presents itself to the surgeon in the ab-

[1]Rectal Insufflation of Hydrogen Gas an Infallible Test in the Diagnosis of Visceral Injury of the Gastro-intestinal Canal in Penetrating Wounds of the Abdomen. By N. Senn, M. D., Ph. D. (Milwaukee, Wis.)—*Journal of the American Medical Association*, June 23 and 30, 1888.

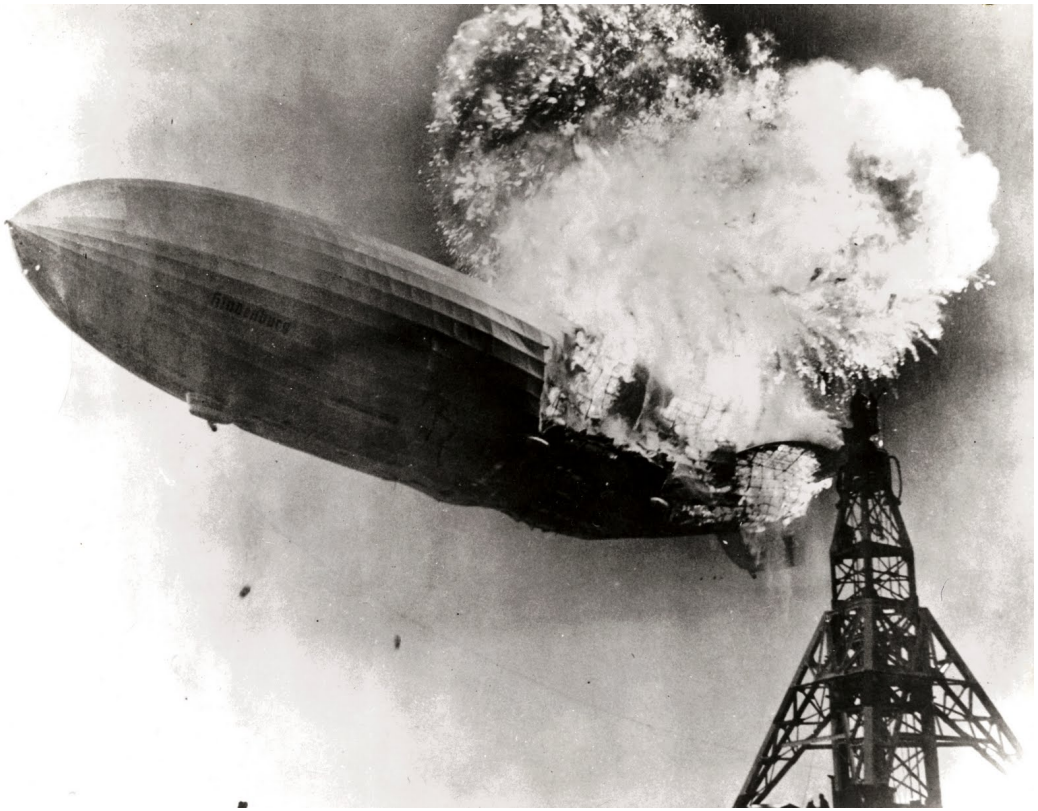
(190)

Pilcher JE
水素ガスの直腸注入による穿孔診断
（分子状水素をはじめて生体に利用）

水素の効果を示したものではない

大量投与においても毒性を認めず
安全に利用できた

1937年：ヒンデンブルグ号事故とその原因



事故原因が「水素ガスの引火」と流布されたため、水素利用が急激に低下する原因となった事故。

水素飛行船の安全神話の崩壊と水素飛行船の禁止

当然、医学利用も衰退。

現在、その原因は船体外皮の「酸化鉄・アルミニウム混合塗料からの静電気と機体連結ミス説」が有力。
（テルミット反応）

この場合はヘリウムでも船体が炎上

水素が極端に危険というわけではなかった
（水素≒爆発のイメージの原因）

1969:正常人における水素ガスの発生

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE ARCHIVE

Production and Excretion of Hydrogen Gas in Man

Michael D. Levitt, M.D.

N Engl J Med 1969; 281:122-127 | July 17, 1969 | DOI: 10.1056/NEJM196907172810303

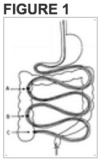
Abstract

Technics employing intestinal infusions of gas were used to study H_2 production in the human intestine. The volume of H_2 in the bowel of 10 normal subjects varied from 0.06 to 29 ml. H_2 production, which averaged 0.24 ml per minute in the fasting state, sharply increased after intestinal instillation of lactose to a mean peak rate of 1.6 ml per minute. Ingestion of food also increased H_2 production by seven-fold to 30-fold. In the normal intestine, more than 99 per cent of H_2 production was colonic, but small-bowel production was increased in a patient with excessive numbers of small-bowel bacteria. H_2 production in man is primarily dependent upon the delivery of ingested, fermentable substrates to an abundant intestinal flora that normally is present only in the colon.

A mean of 14 per cent of the total H_2 production was excreted by the lungs, and rates of breath H_2 excretion and H_2 production correlated well ($r = 0.94$). Respiratory H_2 excretion can therefore be used as an indicator of intestinal H_2 production.

MEDIA IN THIS ARTICLE

FIGURE 1



Schematic Representation of the Position of the Triple-Lumen Tube during the Constant Perfusion Studies.

10人の腸内の水素ガス産生を調査

平均:0.06～29ml/分
平均:0.24ml/分
腸に乳糖注入時平均:1.6ml/分
食事によって7～30倍に増加
平均14%が肺から排泄(他は放屁など)

水素分子は通常血液に溶解している

正常な腸で水素ガスは99%以上が結腸で産生
小腸に過剰の腸内細菌を持った患者では小腸での産生が増加

よって・・・

水素は無作用？ VS 実は体内で作用している？
体内の抗酸化作用の一翼？

1975:水素の扁平上皮癌に対する作用

REPORTS

Hyperbaric hydrogen therapy: a possible treatment for cancer

M Dole, FR Wilson, WP Fife

Science 10 Oct 1975:
Vol. 190, Issue 4210, pp. 152-154
DOI: 10.1126/science.1166304

Abstract

Hairless albino mice with squamous cell carcinoma were exposed to a mixture of 2.5 percent oxygen and 97.5 percent hydrogen at a total pressure of 8 atmospheres for periods up to 2 weeks in order to see if a free radical decay catalyzer, such as hydrogen, would cause a regression of the skin tumors. Marked aggression of the tumors was found, leading to the possibility that hyperbaric hydrogen therapy might also prove to be of significance in the treatment of other types of cancer.

M Dole
マウス扁平上皮癌に水素ガスを利用

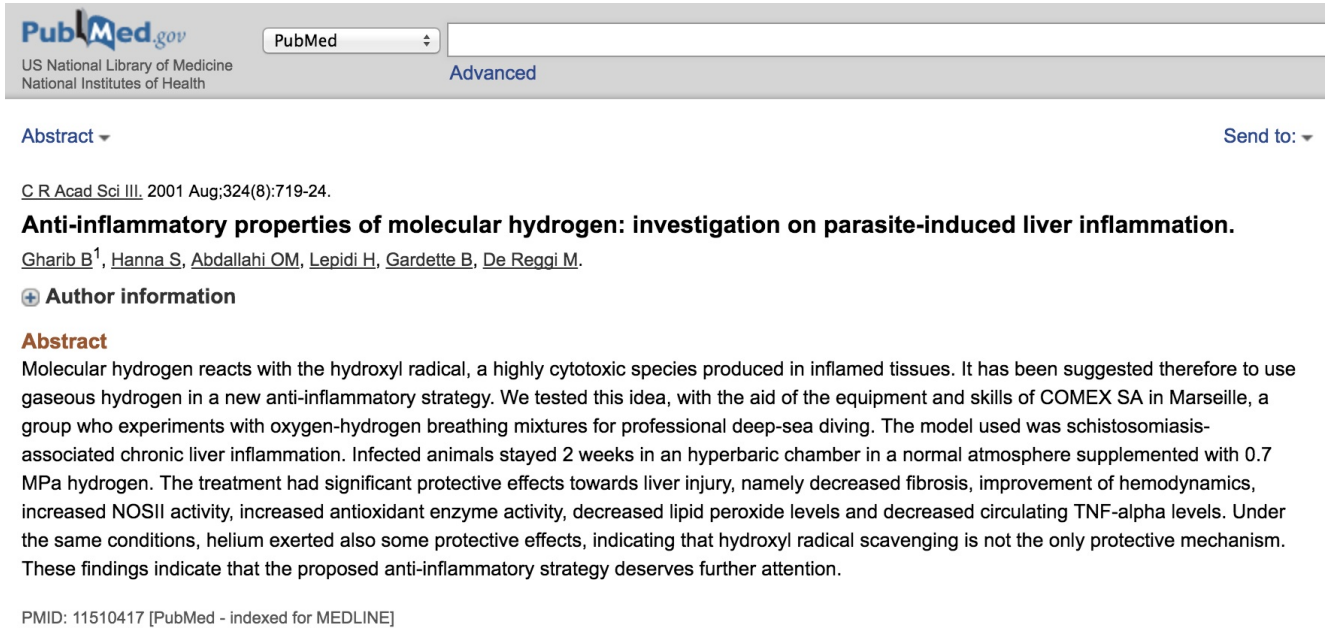
97.5% 8atmという高濃度/高圧ガス

水素は抗酸化物質であるという認識

水素に抗がん作用の可能性

作用機序については言及せず

2001:肝炎に対する水素の抗炎症作用



PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Abstract

Send to:

C R Acad Sci III. 2001 Aug;324(8):719-24.

Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation.

Gharib B[1], Hanna S, Abdallahi OM, Lepidi H, Gardette B, De Reggi M.

Author information

Abstract

Molecular hydrogen reacts with the hydroxyl radical, a highly cytotoxic species produced in inflamed tissues. It has been suggested therefore to use gaseous hydrogen in a new anti-inflammatory strategy. We tested this idea, with the aid of the equipment and skills of COMEX SA in Marseille, a group who experiments with oxygen-hydrogen breathing mixtures for professional deep-sea diving. The model used was schistosomiasis-associated chronic liver inflammation. Infected animals stayed 2 weeks in an hyperbaric chamber in a normal atmosphere supplemented with 0.7 MPa hydrogen. The treatment had significant protective effects towards liver injury, namely decreased fibrosis, improvement of hemodynamics, increased NOSII activity, increased antioxidant enzyme activity, decreased lipid peroxide levels and decreased circulating TNF-alpha levels. Under the same conditions, helium exerted also some protective effects, indicating that hydroxyl radical scavenging is not the only protective mechanism. These findings indicate that the proposed anti-inflammatory strategy deserves further attention.

PMID: 11510417 [PubMed - indexed for MEDLINE]

水素吸入が住血吸虫感染部（炎症部）に対し抗炎症効果

ヒドロキシラジカルと炎症反応の関係性と水素の作用の発表

抗酸化酵素を増加、過酸化脂質レベルを低下、循環レベル**TNFα**を低下

肝組織の繊維化を抑制し、肝損傷に対する有為な保護作用

新しい抗炎症戦略物質として水素ガスを提案した初めての論文

ヒドロキシラジカルへの選択性については言及せず

2007：太田らによる論文

Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

☆1975 Dole

Hyperbaric hydrogen therapy
: A possible treatment for cancer

☆2001 Gharib B

Anti-inflammatory properties of molecular hydrogen
: Investigation on parasite induced liver inflammation

水素の効果を示すもののその理由は不明

水素の作用は選択的な活性酸素の除去

nature.com > Journal home > Table of Contents

Article

Nature Medicine **13**, 688–694 (1 June 2007) | doi:10.1038/nm1577

Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals

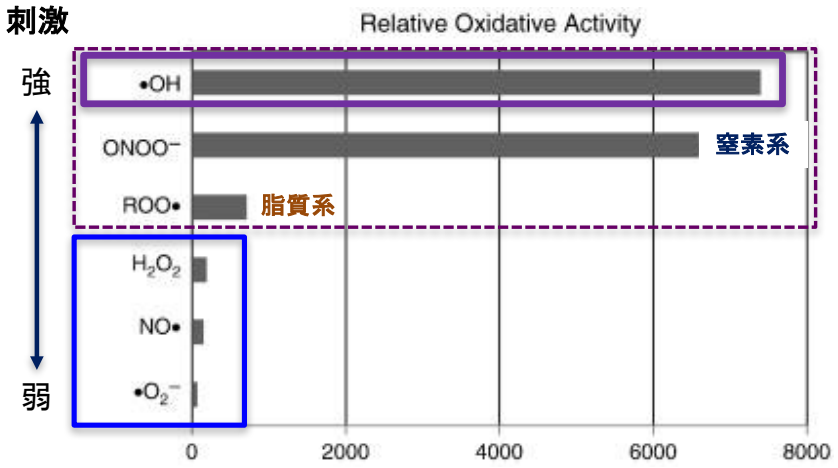
Ikuroh Ohsawa , Masahiro Ishikawa , Kumiko Takahashi , Megumi Watanabe , Kiyomi Nishimaki , Kumi Yamagata , Ken-ichiro Katsura , Yasuo Katayama , Sadamitsu Asoh & Shigeo Ohta

Acute oxidative stress induced by ischemia-reperfusion or inflammation causes serious damage to tissues, and persistent oxidative stress is accepted as one of the causes of many common diseases including cancer. We show here that hydrogen (H2) has potential as an antioxidant in preventive and therapeutic applications. We induced acute oxidative stress in cultured cells by three independent methods. H2 selectively reduced the hydroxyl radical, the most cytotoxic of reactive oxygen species (ROS), and effectively protected cells; however, H2 did not react with other ROS, which possess physiological roles. We used an acute rat model in which oxidative stress damage was induced in the brain by focal ischemia and reperfusion. The inhalation of H2 gas markedly suppressed brain injury by buffering the effects of oxidative stress. Thus H2 can be used as an effective antioxidant therapy; owing to its ability to rapidly diffuse across membranes, it can reach and react with cytotoxic ROS and thus protect against oxidative damage.

ROSの活性度と生理活性/細胞傷害

TROS
Toxic ROS
細胞障害作用
活性：高

BROS
Biological ROS
生理活性作用
活性：低



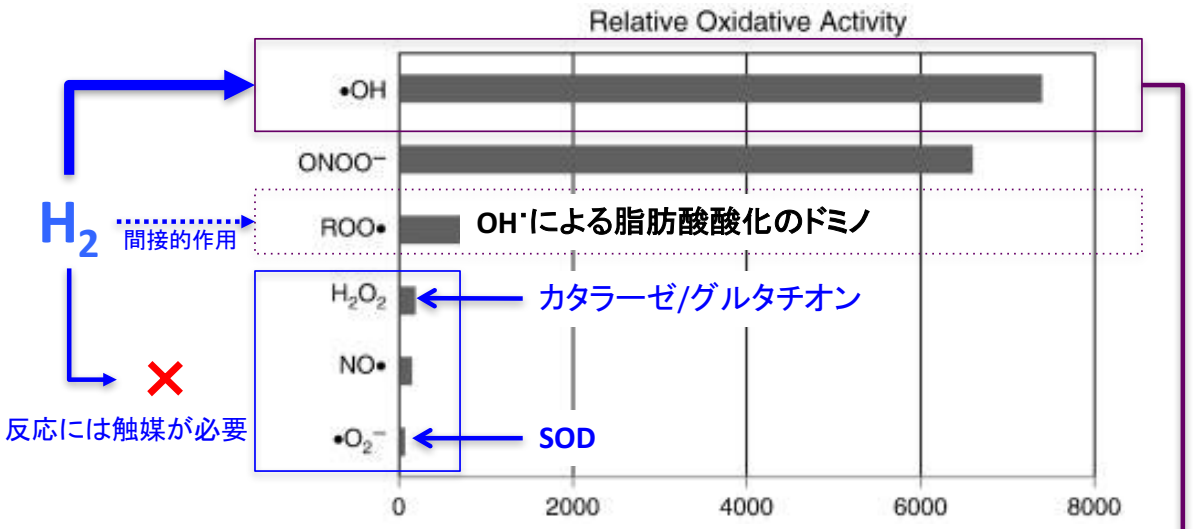
治療ターゲット

除去により悪影響

抗酸化治療にはターゲット選択性が重要

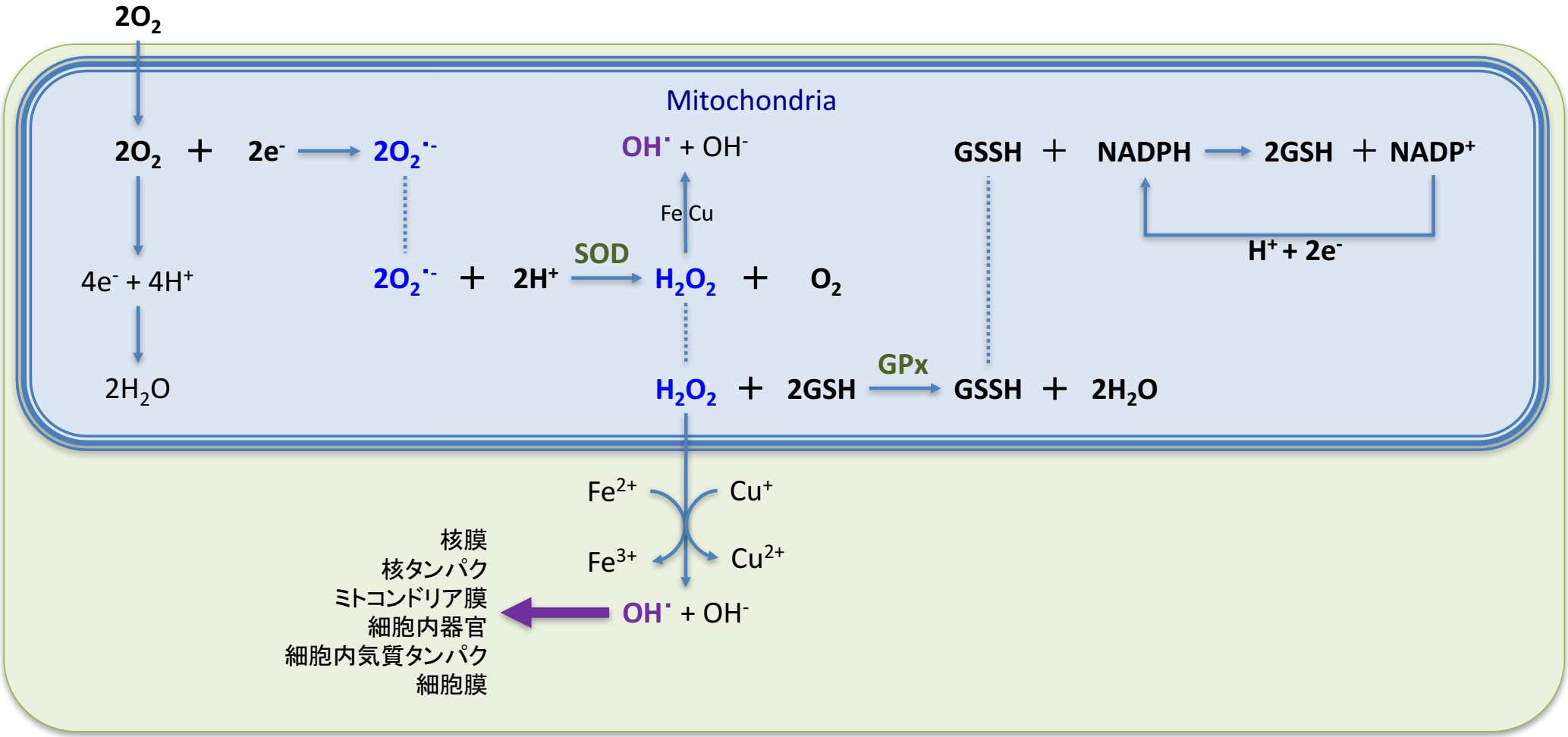
選択的抗酸化作用

活性酸素の善玉/悪玉理論と水素の選択性

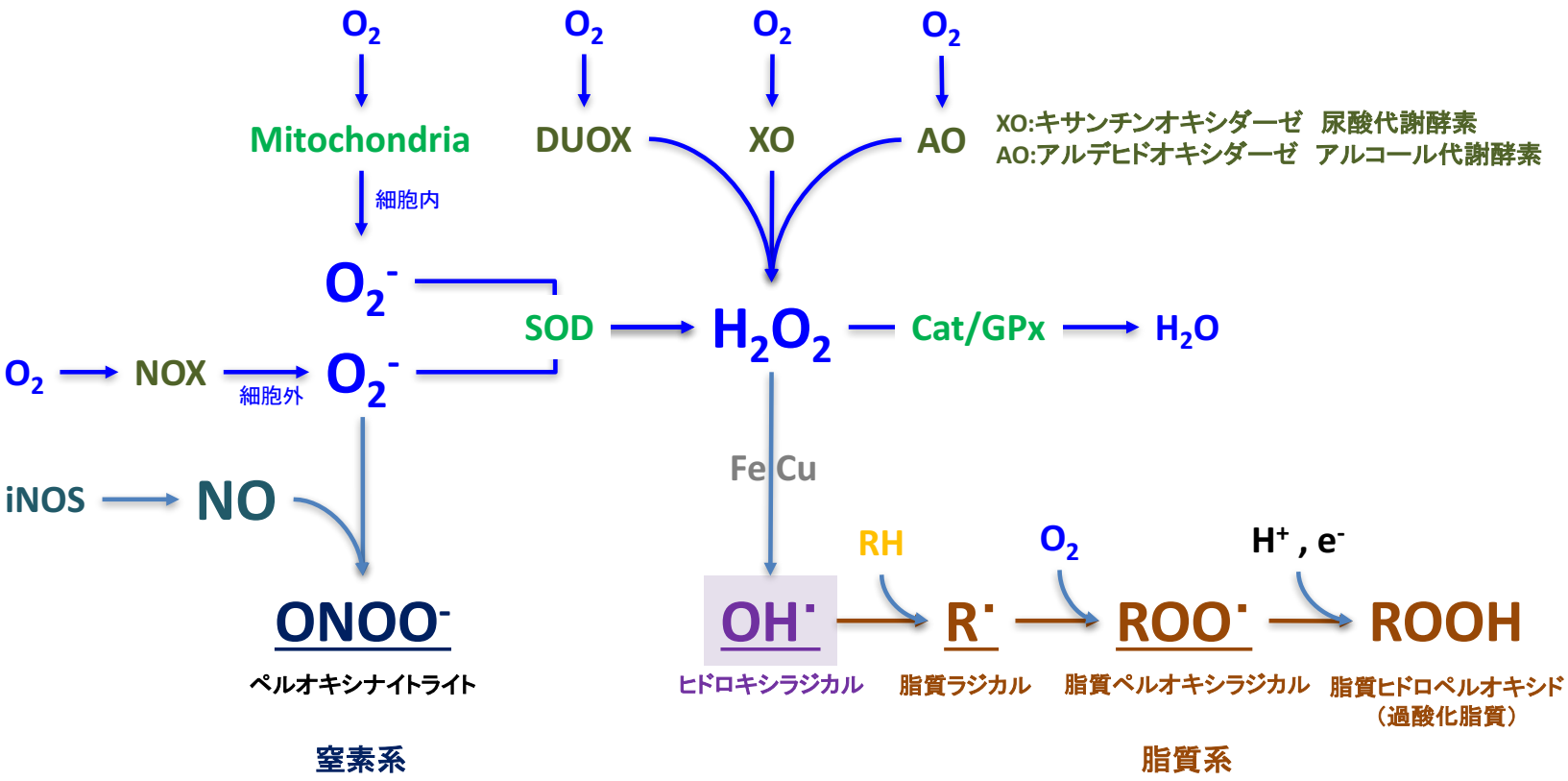


生体内の抗酸化酵素が除去できない活性酸素
生理活性型活性酸素と比べ物にならない酸化活性

ミトコンドリアと活性酸素

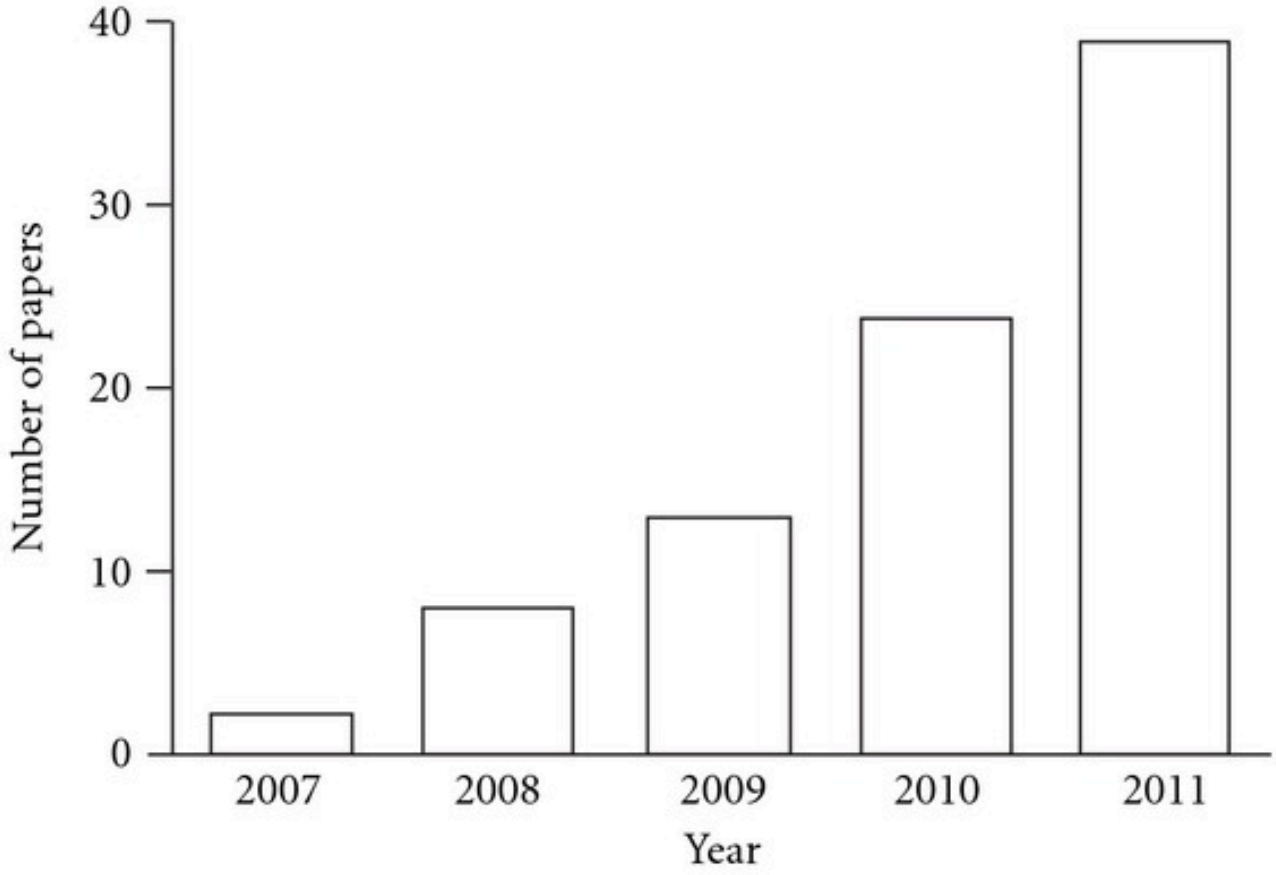


生体における活性酸素の発生



不飽和脂肪酸

2007年以降の水素論文数



2007年以降の主な論文/臨床試験

2013:水素分子がTNFα誘導性細胞障害を抑制

Mol Cell Biochem. 2013 Jan;373(1-2):1-9. doi: 10.1007/s11010-012-1450-4. Epub 2012 Dec 1.

Treatment with hydrogen molecule alleviates TNFα-induced cell injury in osteoblast.

Cai WW[1], Zhang MH, Yu YS, Cai JH.

Author information

[1]The Centre of Drug Safeguard, Chinese People's Liberation Army General Hospital, Beijing, People's Republic of China.

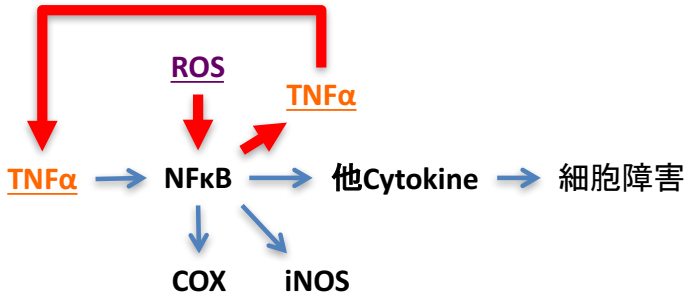
Abstract

Tumor necrosis factor-alpha (TNFα) plays a crucial role in inflammatory diseases such as rheumatoid arthritis and postmenopausal osteoporosis. Recently, it has been demonstrated that hydrogen gas, known as a novel antioxidant, can exert therapeutic anti-inflammatory effect in many diseases. In this study, we investigated the effect of treatment with hydrogen molecule (H(2)) on TNFα-induced cell injury in osteoblast. The osteoblasts isolated from neonatal rat calvariae were cultured. It was found that TNFα suppressed cell viability, induced cell apoptosis, suppressed Runx2 mRNA expression, and inhibited alkaline phosphatase activity, which was reversed by co-incubation with H(2). Incubation with TNFα-enhanced intracellular reactive oxygen species (ROS) formation and malondialdehyde production increased NADPH oxidase activity, impaired mitochondrial function marked by increased mitochondrial ROS formation and decreased mitochondrial membrane potential and ATP synthesis, and suppressed activities of antioxidant enzymes including SOD and catalase, which were restored by co-incubation with H(2). Treatment with H(2) inhibited TNFα-induced activation of NFκB pathway. In addition, treatment with H(2) inhibited TNFα-induced nitric oxide (NO) formation through inhibiting iNOS activity. Treatment with H(2) inhibited TNFα-induced IL-6 and ICAM-1 mRNA expression. In conclusion, treatment with H(2) alleviates TNFα-induced cell injury in osteoblast through abating oxidative stress, preserving mitochondrial function, suppressing inflammation, and enhancing NO bioavailability.

PMID: 23212446 [PubMed - indexed for MEDLINE]

免疫発動/炎症とROS

- **NFκB経路でのTNFα誘導を遮断**
- **iNOS活性の阻害によるNO抑制**
- **IL-6 mRNAの発現を抑制**
- **ICAM-1 mRNAの発現を抑制**
- **ミトコンドリア機能の維持**



2014:心肺停止後に対する水素ガス吸入の効果

Circulation. 2014 Dec 9;130(24):2173-80. doi: 10.1161/CIRCULATIONAHA.114.011848. Epub 2014 Nov 3.

Hydrogen inhalation during normoxic resuscitation improves neurological outcome in a rat model of cardiac arrest independently of targeted temperature management.

Hayashida K[1], Sano M[2], Kamimura N[1], Yokota T[1], Suzuki M[1], Ohta S[1], Fukuda K[1], Hori S[1].

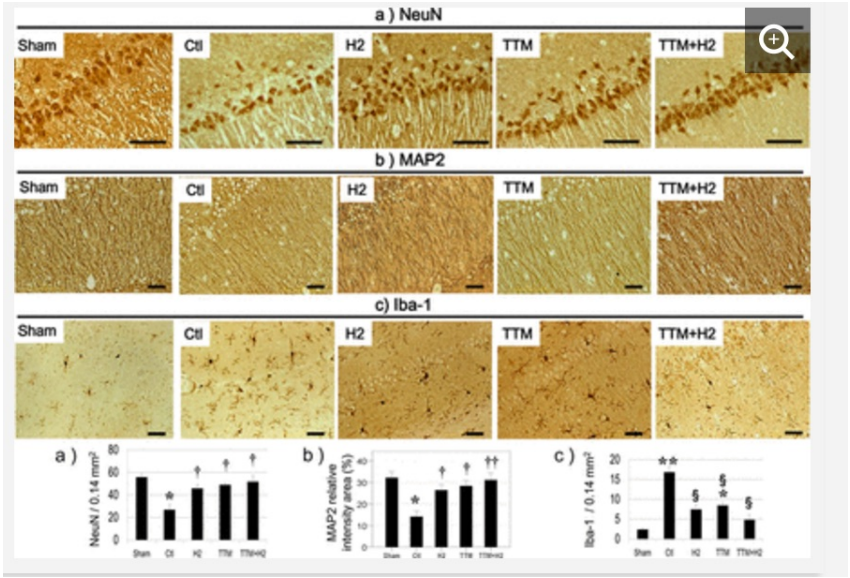
Author information

Abstract

BACKGROUND: We have previously shown that hydrogen (H2) inhalation, begun at the start of hyperoxic cardiopulmonary resuscitation, significantly improves brain and cardiac function in a rat model of cardiac arrest. Here, we examine the effectiveness of this therapeutic approach when H2 inhalation is begun on the return of spontaneous circulation (ROSC) under normoxic conditions, either alone or in combination with targeted temperature management (TTM).

METHODS AND RESULTS: Rats were subjected to 6 minutes of ventricular fibrillation cardiac arrest followed by cardiopulmonary resuscitation. Five minutes after achieving ROSC, post-cardiac arrest rats were randomized into 4 groups: mechanically ventilated with 26% O2 and normothermia (control); mechanically ventilated with 26% O2, 1.3% H2, and normothermia (H2); mechanically ventilated with 26% O2 and TTM (TTM); and mechanically ventilated with 26% O2, 1.3% H2, and TTM (TTM+H2). Animal survival rate at 7 days after ROSC was 38.4% in the control group, 71.4% in the H2 and TTM groups, and 85.7% in the TTM+H2 group. Combined therapy of TTM and H2 inhalation was superior to TTM alone in terms of neurological deficit scores at 24, 48, and 72 hours after ROSC, and motor activity at 7 days after ROSC. Neuronal degeneration and microglial activation in a vulnerable brain region was suppressed by both TTM alone and H2 inhalation alone, with the combined therapy of TTM and H2 inhalation being most effective.

CONCLUSIONS: H2 inhalation was beneficial when begun after ROSC, even when delivered in the absence of hyperoxia. Combined TTM and H2 inhalation was more effective than TTM alone.



・行動量/認知機能の低下を抑制
・神経細胞死/炎症反応が著明に低下

水素吸入により
・神経細胞壊死は減少
・海馬/大脳皮質ミクログリア活性を抑制

2015:出血性ショックによる腸粘膜損傷を水素点滴が抑制

Int J Clin Exp Med. 2015 May 15;8(5):7620-6. eCollection 2015.

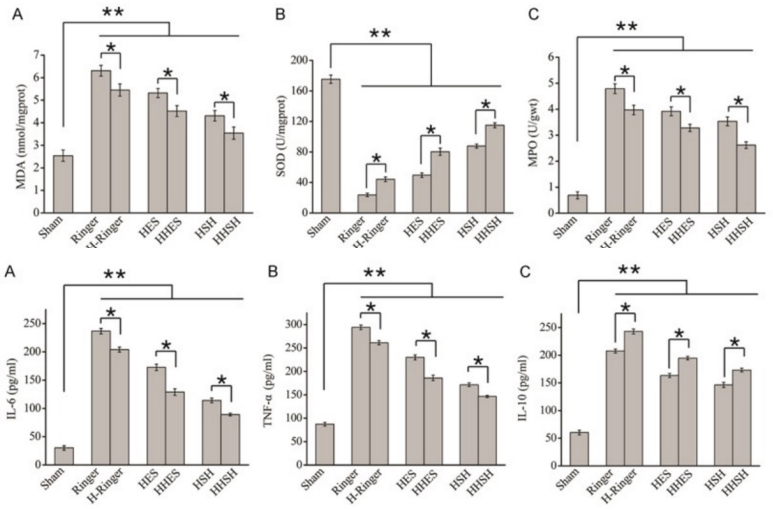
Three hydrogen-rich solutions protect against intestinal injury in uncontrolled hemorrhagic shock.

Du Z[1], Liu J[2], Jia H[2], Xu W[2], Zhao X[3].

Author information

Abstract

Intestinal tissue got largely decreased blood supply in uncontrolled hemorrhagic shock, because of limited blood mainly supporting brain, heart, kidney etc. This makes intestine as the primary injury target after uncontrolled hemorrhagic shock. However, limited studies focus on how to protect intestine against hemorrhagic shock. Ringer's solution, pentoxifylline and hypertonic saline are widely used to resuscitate in haemorrhagic shock and sepsis tissue injury. Evidence showed that hydrogen inhibited inflammation and reduced oxidative damage. Here we tested the hypothesis whether hydrogen rich Ringer's, pentoxifyline and hypertonic saline solutions increase the benefit in protecting small intestine from injury in uncontrolled hemorrhagic shock rat model. We tested the anti-inflammation effect of H-Ringer's, HHES and HHSH administration. We found hydrogen-rich solutions treatment groups showed the decreased MDA, MPO, IL-6 and TNF-α levels, and increased SOD, IL-10 comparing with those of non-hydrogen solutions administration groups. Our histological results showed that these three solutions with saturation hydrogen alleviated the intestinal injury including the intact intestinal villi and less neutrephil infiltration. Our results indicate that these three hydrogen-rich solutions can protect intestinal injure after uncontrolled hemorrhagic shock. The protective effect might be through inhibiting proinflammatory factors, promoting anti-inflammatory cytokines and reducing inflammatory cells infiltration. Our study has potential clinical importance of uncontrolled hemorrhagic shock patient's resuscitation.



・出血性ショックによって起こる消化管粘膜の虚血障害に対し、水素を投与
・組織学的には腸絨毛損傷の軽減、好中球浸潤減少
・水素投与群でMDA, MPO, IL-6, TNFαの低下（炎症性サイトカイン増加）
・水素投与群でSOD, IL-10の増加（抗炎症性サイトカイン/抗酸化物質増加）

付録 2016:DJ-1遺伝子の変異によるパーキンソン病の発症

Sci Rep. 2016 Jul 29;6:30793. doi: 10.1038/srep30793.

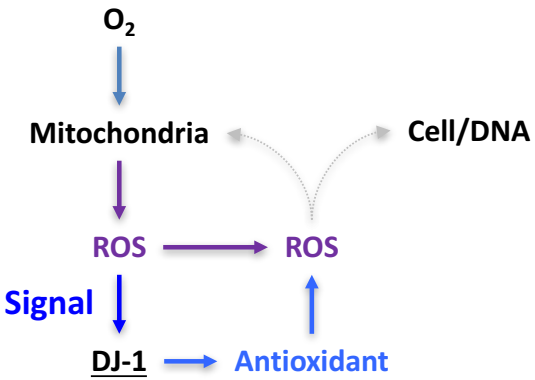
Oxidation and interaction of DJ-1 with 20S proteasome in the erythrocytes of early stage Parkinson's disease patients.

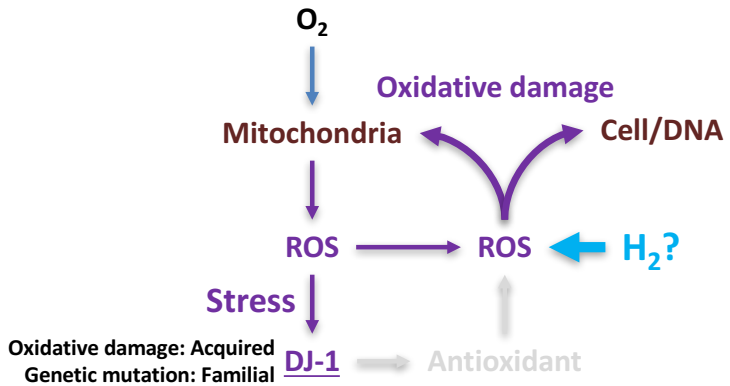
Saito Y[1,2], Akazawa-Ogawa Y[2], Matsumura A[3], Saigoh K[4], Itoh S[5], Sutou K[1], Kobayashi M[1], Mita Y[1], Shichiri M[2], Hisahara S[3], Hara Y[6], Fujimura H[7], Takamatsu H[5], Hagihara Y[2], Yoshida Y[2], Hamakubo T[8], Kusunoki S[4], Shimohama S[3], Noguchi N[1].

Author information

Abstract

Parkinson's disease (PD) is a progressive, age-related, neurodegenerative disorder, and oxidative stress is an important mediator in its pathogenesis. DJ-1, the product of the causative gene of a familial form of PD, plays a significant role in anti-oxidative defence to protect cells from oxidative stress. DJ-1 undergoes preferential oxidation at the cysteine residue at position 106 (Cys-106) under oxidative stress. Here, using specific antibodies against Cys-106-oxidized DJ-1 (oxDJ-1), it was found that the levels of oxDJ-1 in the erythrocytes of unmedicated PD patients (n = 88) were higher than in those of medicated PD patients (n = 62) and healthy control subjects (n = 33). Elevated oxDJ-1 levels were also observed in a non-human primate PD model. Biochemical analysis of oxDJ-1 in erythrocyte lysates showed that oxDJ-1 formed dimer and polymer forms, and that the latter interacts with 20S proteasome. These results clearly indicate a biochemical alteration in the blood of PD patients, which could be utilized as an early diagnosis marker for PD.





2016:パーキンソン病に対する多施設二重盲検試験

BMC Neurol. 2016 May 12;16(1):66. doi: 10.1186/s12883-016-0589-0.

A randomized double-blind multi-center trial of hydrogen water for Parkinson's disease: protocol and baseline characteristics.

Yoritaka A[1,2], Abe T[3], Ohtsuka C[4], Maeda T[5], Hirayama M[6], Watanabe H[7], Saiki H[8], Oyama G[9], Fukae J[10], Shimo Y[9], Hatano T[9], Kawajiri S[11], Okuma Y[11], Machida Y[12], Miwa H[12], Suzuki C[13], Kazama A[14], Tomiyama M[15], Kihara T[16], Hirasawa M[17], Shimura H[18], Hattori N[9].

Author information

Abstract

BACKGROUND: Our previous randomized double-blind study showed that drinking hydrogen (H2) water for 48 weeks significantly improved the total Unified Parkinson's Disease Rating Scale (UPDRS) score of Parkinson's disease (PD) patients treated with levodopa. We aim to confirm this result using a randomized double-blind placebo-controlled multi-center trial.

METHODS: Changes in the total UPDRS scores from baseline to the 8(th), 24(th), 48(th), and 72(nd) weeks, and after the 8(th) week, will be evaluated. The primary endpoint of the efficacy of this treatment in PD is the change in the total UPDRS score from baseline to the 72(nd) week. The changes in UPDRS part II, UPDRS part III, each UPDRS score, PD Questionnaire-39 (PDQ-39), and the modified Hoehn and Yahr stage at these same time-points, as well as the duration until the protocol is finished because additional levodopa is required or until the disease progresses, will also be analyzed. Adverse events and screening laboratory studies will also be examined. Participants in the hydrogen water group will drink 1000 mL/day of H2 water, and those in the placebo water group will drink normal water. One-hundred-and-seventy-eight participants with PD (89 women, 89 men; mean age: 64.2 [SD 9.2] years, total UPDRS: 23.7 [11.8], with levodopa medication: 154 participants, without levodopa medication: 24 participants; daily levodopa dose: 344.1 [202.8] mg, total levodopa equivalent dose: 592.0 [317.6] mg) were enrolled in 14 hospitals and were randomized.

パーキンソン症に対して行われた大規模な二重盲検試験で有効性を確認

H_2 5mM含有の水素水を1L/day 8weeks

評価

UPDRS（unified Parkinson‘s disease rating scale）において効果を確認

水素投与により、パーキンソン病の進行を抑制しうる

Clinical trials registered in Japan as of June, 2015

Med Gas Res. 2015; 5: 12.
Published online 2015 Oct 19

Clinical trials registered in Japan as of June, 2015

Date	Disease	Affiliation	Status
7/16/2008	Interstitial cystitis	Koshinkai Hosp.	Finished[201]
8/21/2008	Impaired glucose tolerance and impaired fasting glycaemia	Digestive tract internal medicine, Kyoto Prefectural University of Medicine	Finished [236].
7/17/2009	Mild cognitive impairment	Neuropsychiatry, Tsukuba Univ.	Finished
1/11/2011	Chronic hemodialysis	Nephrology, Fukushima Medical University	Trial in progress
6/2/2011	Acute cerebral infarction	Neurosurgery, Self Defense Medical College	Calling for participants[106]
9/30/2011	Normal adults	Faculty of Health Sciences, Kyorin Univ.	Finished
12/4/2011	Acute myocardial infarction	Cardiology, Keio Univ.	Calling for participants
3/14/2012	Parkinson's disease	Neurology, Juntendo Univ.	Finished [96]
10/16/2012	Multiple system atrophy, Progressive supranuclear palsy	Neurology, Juntendo Univ.	Trial in progress
2/13/2013	Parkinson's disease	Neurology, Juntendo Univ.	Calling for participants
5/1/2013	Chronic obstructive pulmonary disease	Respiratory Medicine, Juntendo Univ.	Trial in progress
5/20/2013	Hepatitis and liver cirrhosis	Gastroenterology and Hepatology, Okayama Univ.	In preparation
11/22/2013	Post cardiac arrest syndrome	Emergency and Critical care medicine, Keio Univ.	Calling for participants
2/22/2014	Eye disease	Ophthalmology, Nippon Medical school	Finished
7/1/2014	Acute myocardial infarction	Cardiology, National Center for Global Health and Medicine	Calling for participants
7/29/2014	Subarachnoid hemorrhage	Neurosurgery, Self Defense Medical College	Calling for participants [113]
8/1/2014	Lung transplantation	General thoracic surgery, Osaka Univ.	Calling for participants
10/27/2014	Retinal artery occlusion	Ophthalmology, Nippon Medical school	Calling for participants
7/3/2015	Type 2 diabetes mellitus	Tokyo Metropolitan Institute of Gerontology	Calling for participants

The department names are shown if they are available in the UMIN clinical trial database

Clinical trials published as of June, 2015

Med Gas Res. 2015; 5: 12.
Published online 2015 Oct 19

Authors/Year	Disease	Sample size	Open-label (OL), double-blind (DB), or single-blind (SB)	Hydrogen administration	Summary of the outcome
Kajiyama et al. [236]/2008	Diabetes mellitus type II	30	DB	Water	Improvement of fractions of low-density lipoprotein (LDL)-cholesterol and a glucose tolerance test.
Nakao et al. [245]/2010	Metabolic syndrome	20	OL	Water	Improvement of urinary markers for oxidative stress such as SOD and TBARS, and increase of high-density lipoprotein (HDL)-cholesterol.
Nakayama et al. [311]/2010	Chronic renal failure	29	OL	Dialysis	Amelioration of hypertension and improvement of markers for oxidative stress and inflammation.
Ito et al. [223]/2011	Inflammatory and mitochondrial myopathies	31	OL/DB	Water	OL: Improvement of the serum lactate/pyruvate ratio in mitochondrial myopathies and the serum matrix metalloproteinse-3 level in polymyositis/dermatomyositis. DB: Improvement of the serum lactate.
Kang et al. [281]/2011	Radiation-induced adverse effects for liver tumors	49	OL	Water	Improvement of quality of life (QOL) scores during radiotherapy. Reduction of blood reactive oxygen metabolites and maintenance of blood oxidation potential.
Ishibashi et al. [218]/2012	Rheumatoid arthritis	20	OL	Water	Improvement of disease activity score for rheumatoid arthritis (DAS28). Decrease of urinary 8-OHdG.
Aoki et al. [224]/2012	Muscle fatigue	10	DB	Water	Improvement of muscle fatigue in young athletes
Li et al. [216]/2013	Pressure skin ulcer	22	OL	Water	Wound size reduction and early recovery from skin pressure ulcer.
Matsumoto et al. [201]/2013	Interstitial cystitis	30	DB	Water	No significant effect on symptoms. Reduction of the bladder pain score in 11 % of patients.
Nagatani et al. [106]/2013	Cerebral ischemia	38	OL	Intravenous infusion	Confirmation of safety of intravenous H_2 infusion. Decrease of MDA-LDL, a serum marker for oxidative stress, in a subset of patients.
Shin et al. [45]/2013	UV-induced skin injury	28	OL	Gas	Prevention and modulation of UV-induced skin inflammation, intrinsic skin aging, and photo aging process through reduction of MMP-1, IL-6, and IL-1b mRNA expression.
Song et al. [243]/2013	Hyperlipidemia	20	OL	Water	Decrease of total serum cholesterol, LDL-cholesterol, apolipoprotein (apo) B100, and apoE
Xia et al. [179]/2013	Chronic hepatitis B	60	DB	Water	Attenuation of oxidative stress
Yoritaka et al. [96]/2013	Parkinson disease	17	DB	Water	Improvement of Total Unified Parkinson's Disease Rating Scale (UPDRS) and exacerbation after termination of H_2 water.
Ishibashi et al. [219]/2014	Rheumatoid arthritis	24	DB	Intravenous saline infusion	Improvement of DAS28. Decrease of serum IL-6, MMP3, CRP, and urinary 8-OHdG.
Ostojic et al. [225]/2014	Sports-related soft tissue injury	36	SB	H2-rich tablets and topical H_2 packs	Decrease of plasma viscosity. Faster recovery from soft tissue injury.
Ostojic et al. [250]/2014	Exercise-induced metabolic acidosis	52	DB	Water	Increased blood alkalinity in physically active men.
Sakai et al. [230]/2014	Vascular endothelial function.	34	DB	Water	Increased flow-mediated dilation of branchial artery, suggesting that H_2 can serve as a modulator of vasomotor function of vasculature.
Song et al. [244]/2015	Hyperlipidemia	68	DB	Water	Down-regulation of plasma levels of total cholesterol, and LDL-cholesterol, followed by increased plasma pre-β -HDL, apoM, and decreased plasma oxidized-LDL, apoB100.

効果が顕著でない理由として
- 種の違い（齧歯類/人）
- 水素濃度/量の調整の困難さ
- 疾患の違い（急性/慢性）

が考えられる（大規模試験の必要性）

オゾン療法の論文からみる水素療法

2011:酸化ストレス度の違いとシグナル

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | Advanced

Abstract | Send to:

Med Gas Res. 2011 Dec 20;1:29. doi: 10.1186/2045-9912-1-29.

Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress?

Sagai M[1], Bocci V.

Author information

Abstract

The potential mechanisms of action of ozone therapy are reviewed in this paper. The therapeutic efficacy of ozone therapy may be partly due the controlled and moderate oxidative stress produced by the reactions of ozone with several biological components. The line between effectiveness and toxicity of ozone may be dependent on the strength of the oxidative stress. As with exercise, it is well known that moderate exercise is good for health, whereas excessive exercise is not.Severe oxidative stress activates nuclear transcriptional factor kappa B (NFκB), resulting in an inflammatory response and tissue injury via the production of COX2, PGE2, and cytokines. However, moderate oxidative stress activates another nuclear transcriptional factor, nuclear factor-erythroid 2-related factor 2 (Nrf2). Nrf2 then induces the transcription of antioxidant response elements (ARE). Transcription of ARE results in the production of numerous antioxidant enzymes, such as SOD, GPx, glutathione-s-transferase(GSTr), catalase (CAT), heme-oxygenase-1 (HO-1), NADPH-quinone-oxidoreductase (NQO-1), phase II enzymes of drug metabolism and heat shock proteins (HSP). Both free antioxidants and anti-oxidative enzymes not only protect cells from oxidation and inflammation but they may be able to reverse the chronic oxidative stress. Based on these observations, ozone therapy may also activate Nrf2 via moderate oxidative stress, and suppress NFκB and inflammatory responses. Furthermore, activation of Nrf2 results in protection against neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Mild immune responses are induced via other nuclear transcriptional factors, such as nuclear factor of activated T-cells (NFAT) and activated protein-1 (AP-1).Additionally, the effectiveness of ozone therapy in vascular diseases may also be explained by the activation of another nuclear transcriptional factor, hypoxia inducible factor-1α (HIF-1a), which is also induced via moderate oxidative stress. Recently these concepts have become widely accepted. The versatility of ozone in treating vascular and degenerative diseases as well as skin lesions, hernial disc and primary root carious lesions in children is emphasized. Further researches able to elucidate whether the mechanisms of action of ozone therapy involve nuclear transcription factors, such as Nrf2, NFAT, AP-1, and HIF-1α are warranted.

PMID: 22185664 [PubMed] PMCID: PMC3298518 **Free PMC Article**

オゾン療法に関する論文

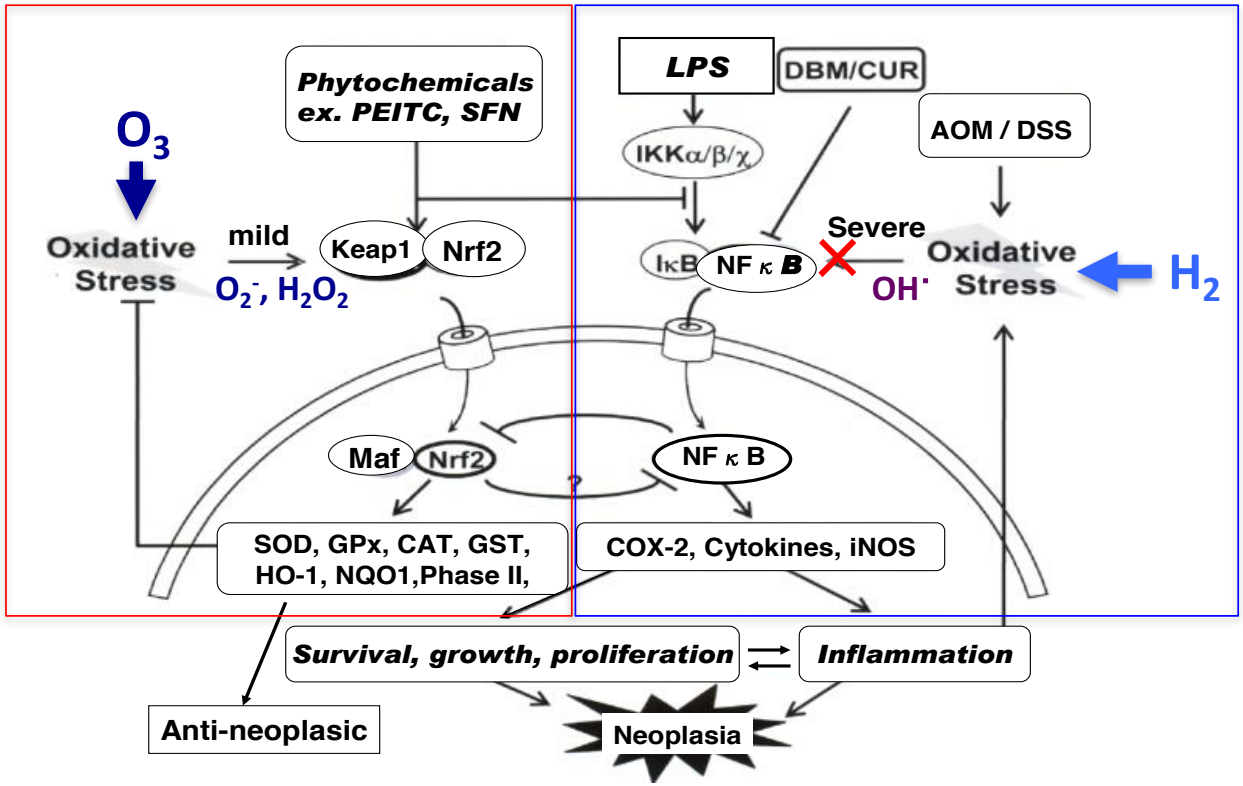
酸化ストレスの強度によって
軽度：Nrf2シグナル
強度：NFκBシグナル
に変化

オゾンによるマイルドな酸化ストレスによってNrf2が活性化
→軽度の酸化ストレスは健康によい

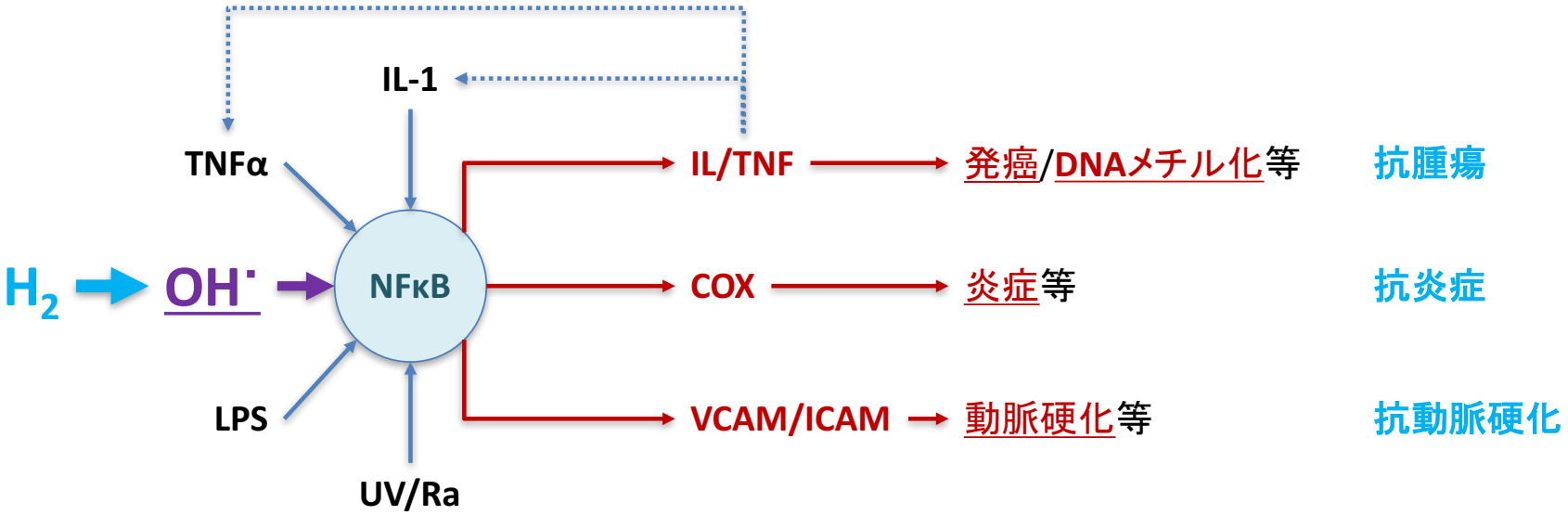
強度の酸化ストレスはNFκBを活性化
→強度の酸化ストレスは除去すべき

酸化（オゾン）療法と抗酸化（水素）療法

共に『気体』を使う治療



NFκBとOH·


IL-1
TNFα
H_2
OH·
NFκB
LPS
UV/Ra
IL/TNF
発癌/DNAメチル化等
抗腫瘍
COX
炎症等
抗炎症
VCAM/ICAM
動脈硬化等
抗動脈硬化

水素とその作用

原子 ― 分子 ― 物質

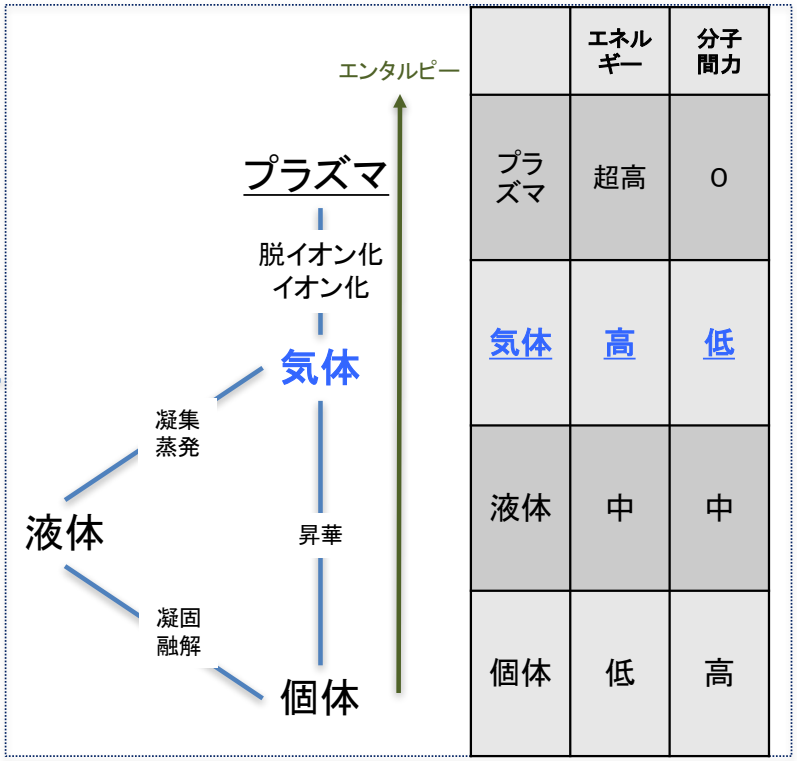
1																	18
1 H 1.0079	2											13	14	15	16	17	2 He 4.0026
3 Li 6.941	4 Be 9.0122											5 B 10.811	6 C 12.011	7 N 14.007	8 O 15.999	9 F 18.998	10 Ne 20.180
11 Na 22.990	12 Mg 24.305	3	4	5	6	7	8	9	10	11	12	13 Al 26.982	14 Si 28.086	15 P 30.974	16 S 32.065	17 Cl 35.453	18 Ar 39.948
19 K 39.098	20 Ca 40.078	21 Sc 44.956	22 Ti 47.867	23 V 50.942	24 Cr 51.996	25 Mn 54.938	26 Fe 55.845	27 Co 58.933	28 Ni 58.693	29 Cu 63.546	30 Zn 65.38	31 Ga 69.723	32 Ge 72.64	33 As 74.922	34 Se 78.96	35 Br 79.904	36 Kr 83.798
37 Rb 85.468	38 Sr 87.62	39 Y 88.906	40 Zr 91.224	41 Nb 92.906	42 Mo 95.96	43 Tc (98)	44 Ru 101.07	45 Rh 102.91	46 Pd 106.42	47 Ag 107.87	48 Cd 112.41	49 In 114.82	50 Sn 118.71	51 Sb 121.76	52 Te 127.60	53 I 126.90	54 Xe 131.29
55 Cs 132.91	56 Ba 137.33	57-71 *	72 Hf 178.49	73 Ta 180.95	74 W 183.84	75 Re 186.21	76 Os 190.23	77 Ir 192.22	78 Pt 195.08	79 Au 196.97	80 Hg 200.59	81 Tl 204.38	82 Pb 207.2	83 Bi 208.98	84 Po (209)	85 At (210)	86 Rn (222)
87 Fr (223)	88 Ra (226)	89-103 #	104 Rf (261)	105 Db (262)	106 Sg (266)	107 Bh (264)	108 Hs (270)	109 Mt (268)	110 Ds (281)	111 Rg (272)	112 Cn (285)	113 Uut (284)	114 Uuq (289)	115 Uup (288)	116 Uuh (291)		118 Uuo (294)

* Lanthanide series	57 La 138.91	58 Ce 140.12	59 Pr 140.91	60 Nd 144.24	61 Pm (145)	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.93	66 Dy 162.50	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.05	71 Lu 174.97
# Actinide series	89 Ac (227)	90 Th 232.04	91 Pa 231.04	92 U 238.03	93 Np (237)	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)

原子 ― 共有結合 / 配位結合 / 金属-金属間結合 → **分子** ― ファンデルワールカ / イオン結合 / 金属結合 / 水素結合 / … → 物質

分子状水素とは「物質化していない水素分子」

物質の四形態

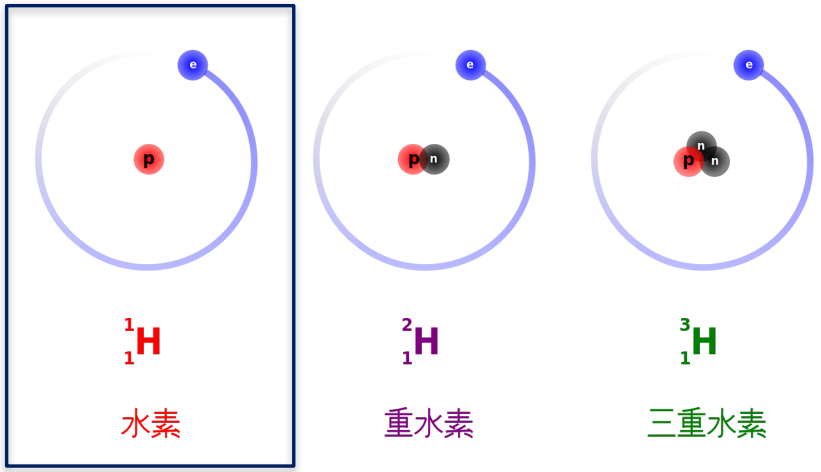


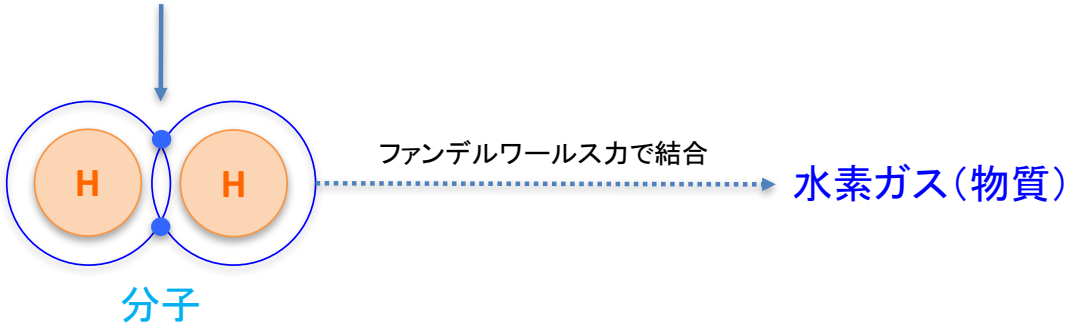
	エネルギー	分子間力
プラズマ	超高	0
気体	高	低
液体	中	中
個体	低	高

・プラズマ水素（電離水素）
・液体水素:沸点（<-252.6℃）
・個体水素:融点（<-259.2℃）

水素とその特性

分類：非金属
族/周期/ブロック：1/1/s
原子量：1.00794
電子配置：$1s^1$
電子殻：1
色：無色
相：気体
密度：0.08988g/L（0℃ 100kPa）
酸化数：1, -1
電気陰性度：2.20
ファンデルワールス半径：120pm



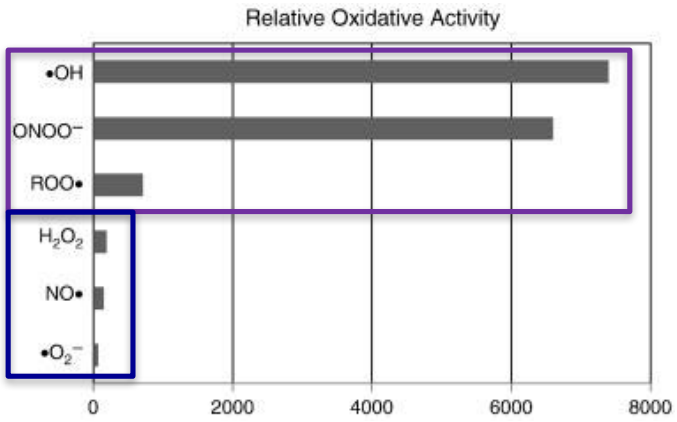


ラジカル（分子）と反応するのは分子状水素

分子状水素のターゲット

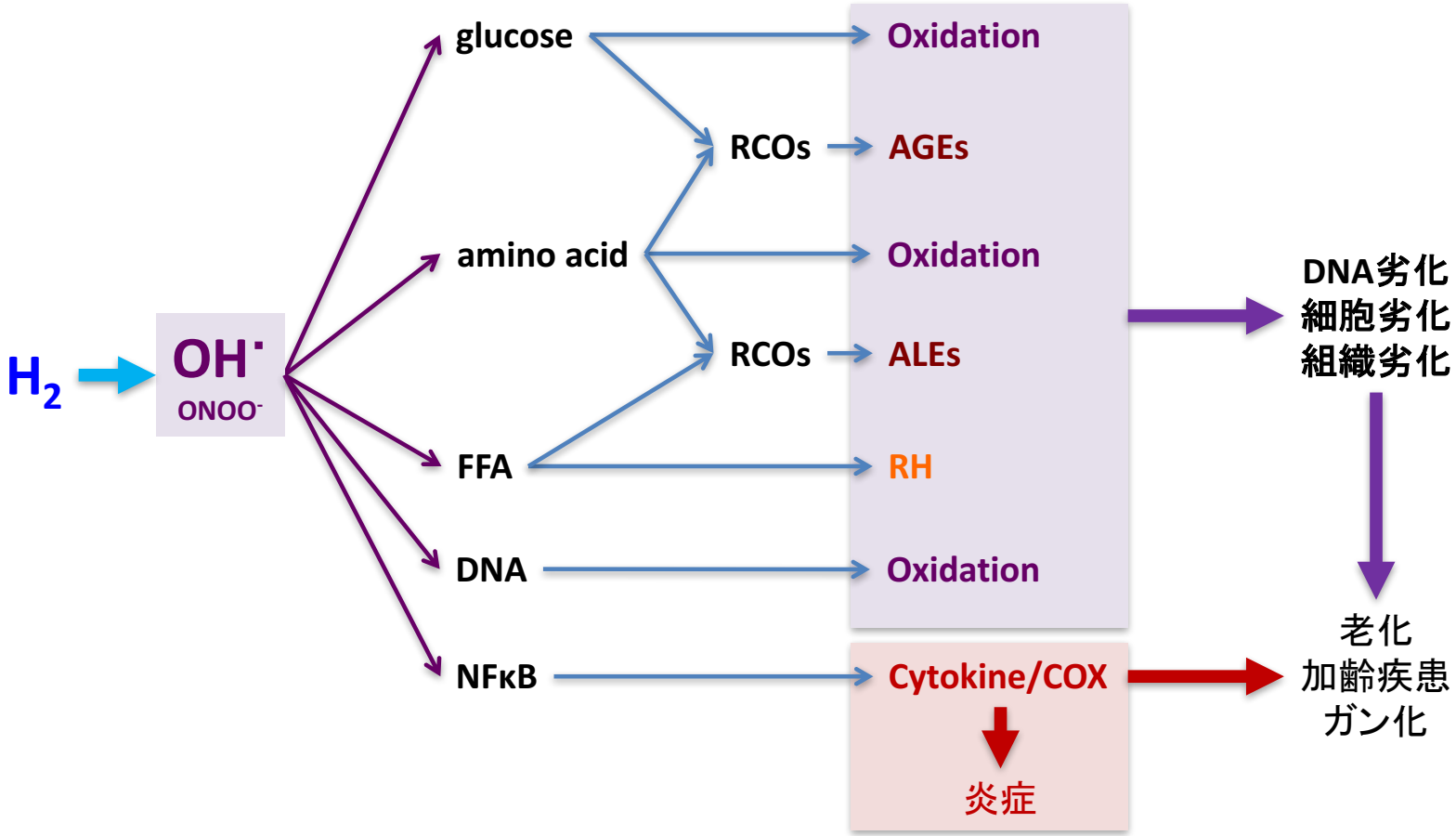
H_2

- $OH\cdot$ → 酸化劣化ストレス
  - $OH\cdot + H_2 \rightarrow H_2O$
- $ONOO^-$ → 酸化劣化ストレス
  - $ONOO^- + H_2 \rightarrow NHO_3$
- × O_2^- → 殺菌作用、ホルモン合成作用
- × H_2O_2 → 殺菌作用、代謝促進作用
- × O_2 → ミトコンドリアでのエネルギー産生
- × $NO\cdot$ → 血管拡張作用

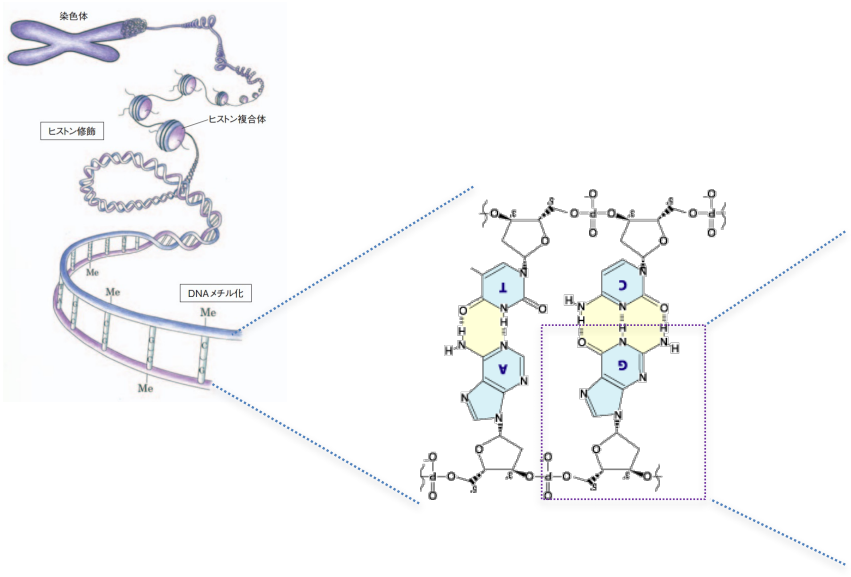


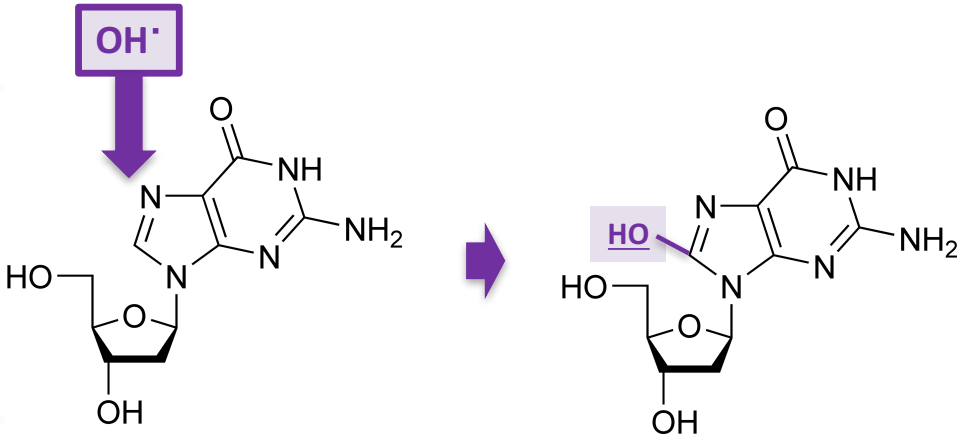
水素の作用はOH·除去による作用

予防効果と抗炎症効果



遺伝子の酸化（例：dGの酸化）





正常なデオキシグアノジン(dG)

アミノ酸の酸化

カルボニル化

アルギニン残基 $\xrightarrow{OH^{\cdot}}$ γグルタミルセミアルデヒド

プロリン残基 $\xrightarrow{OH^{\cdot}}$ ピログルタミン酸

リシン残基 $\xrightarrow{OH^{\cdot}}$ アリシン

ニトロ化

チロシン残基 $\xrightarrow{ONOO^{-}}$ ニトロチロシン

スルホキシド化

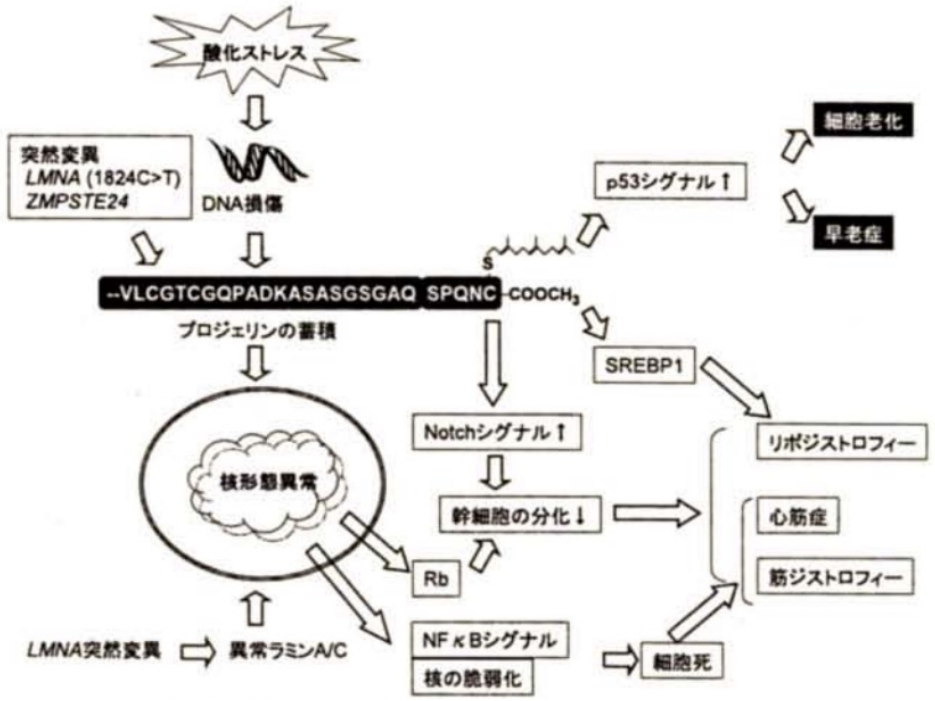
メチオニン残基 $\xrightarrow{OH^{\cdot}}$ メチオニンスルホキシド $\xrightarrow{OH^{\cdot}}$ メチオニンスルホン

スルフェン化

システイン残基 $\xrightarrow{OH^{\cdot}}$ システインスルフェン酸 $\xrightarrow{OH^{\cdot}}$ システインスルフィン酸 $\xrightarrow{OH^{\cdot}}$ システインスルホン酸

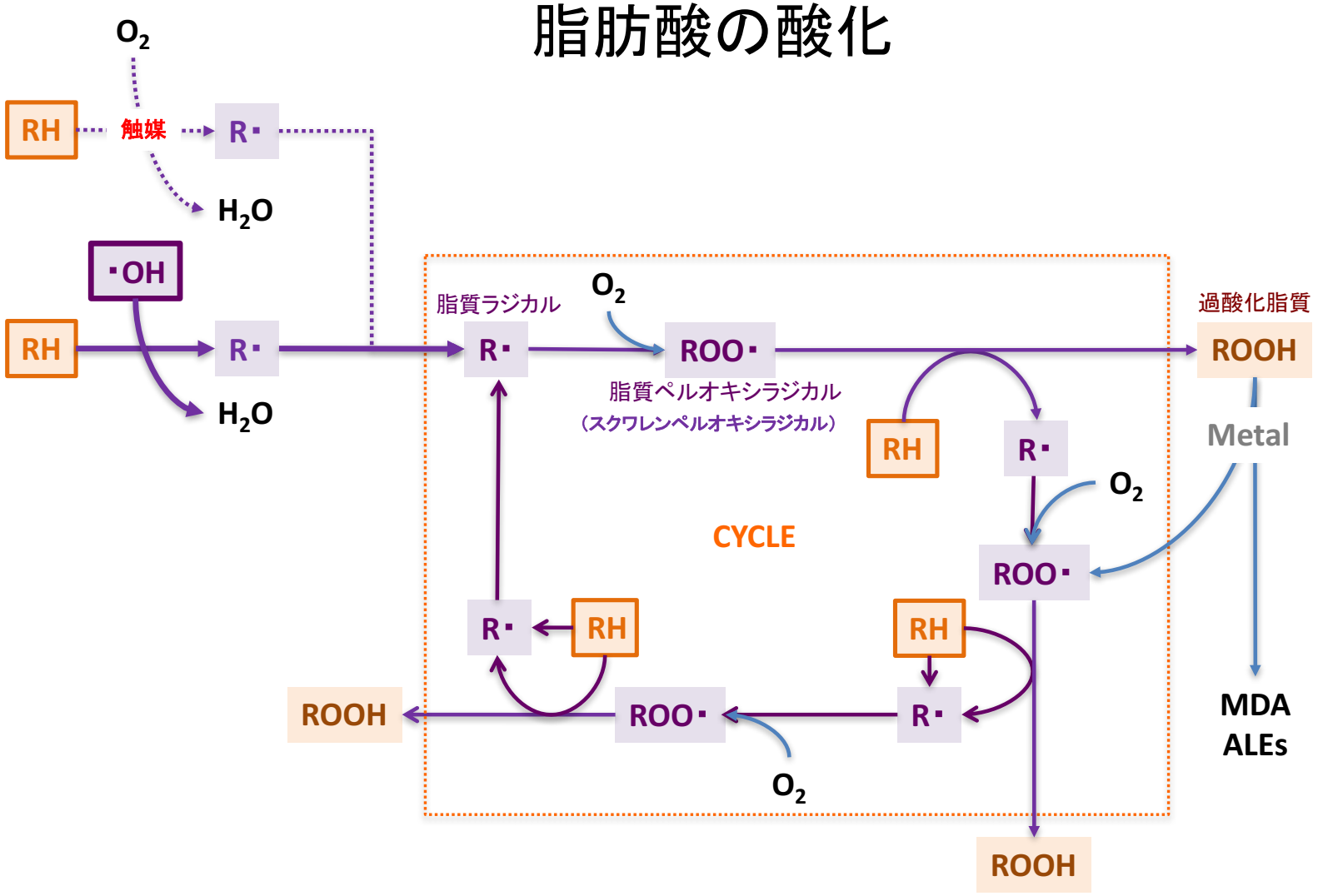
＊システインの抗酸化力は3度の酸化変性反応のため

核ラミンAタンパクの酸化と老化/疾患

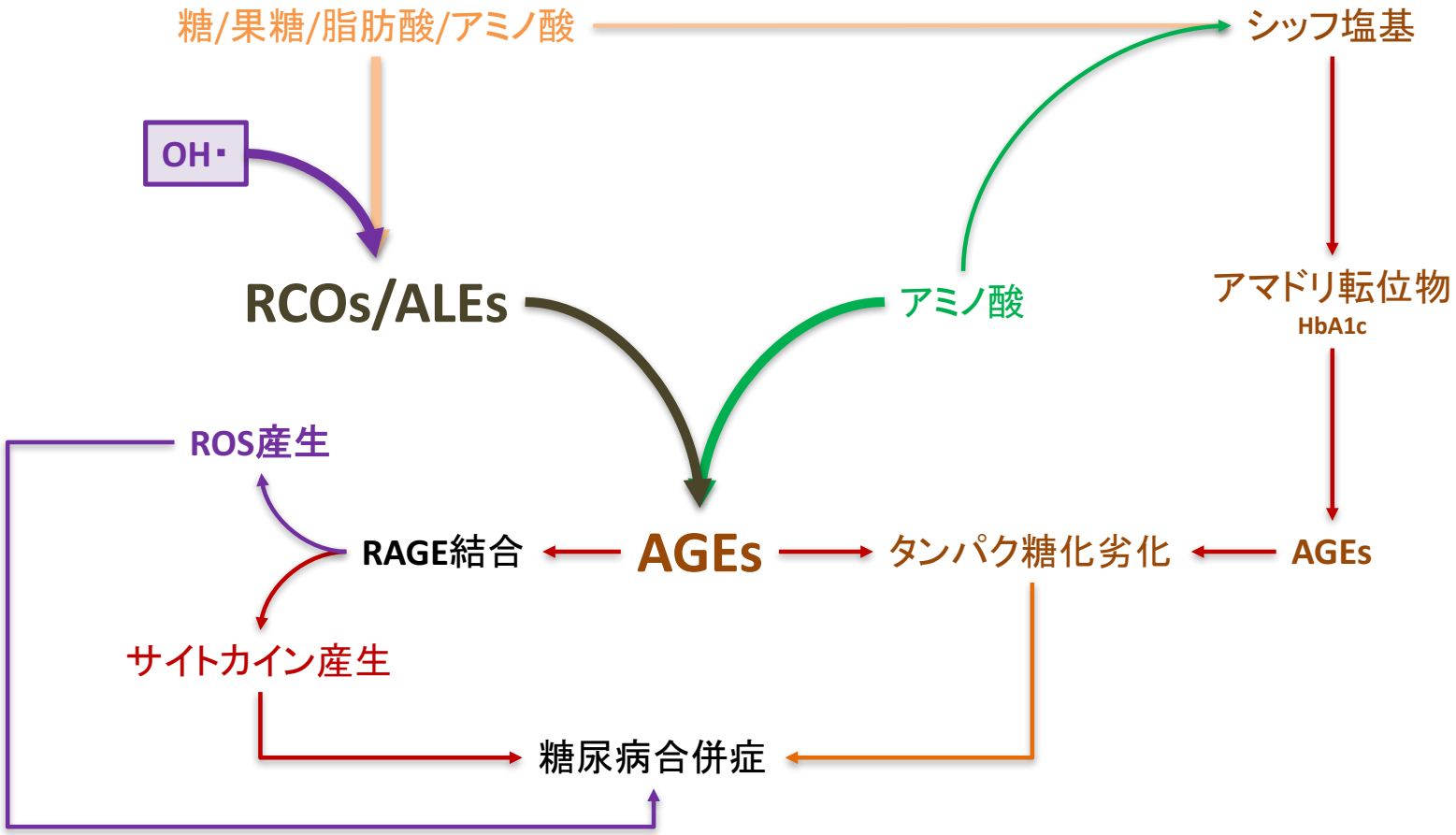


基礎老化研究開(4);3-1 2009より

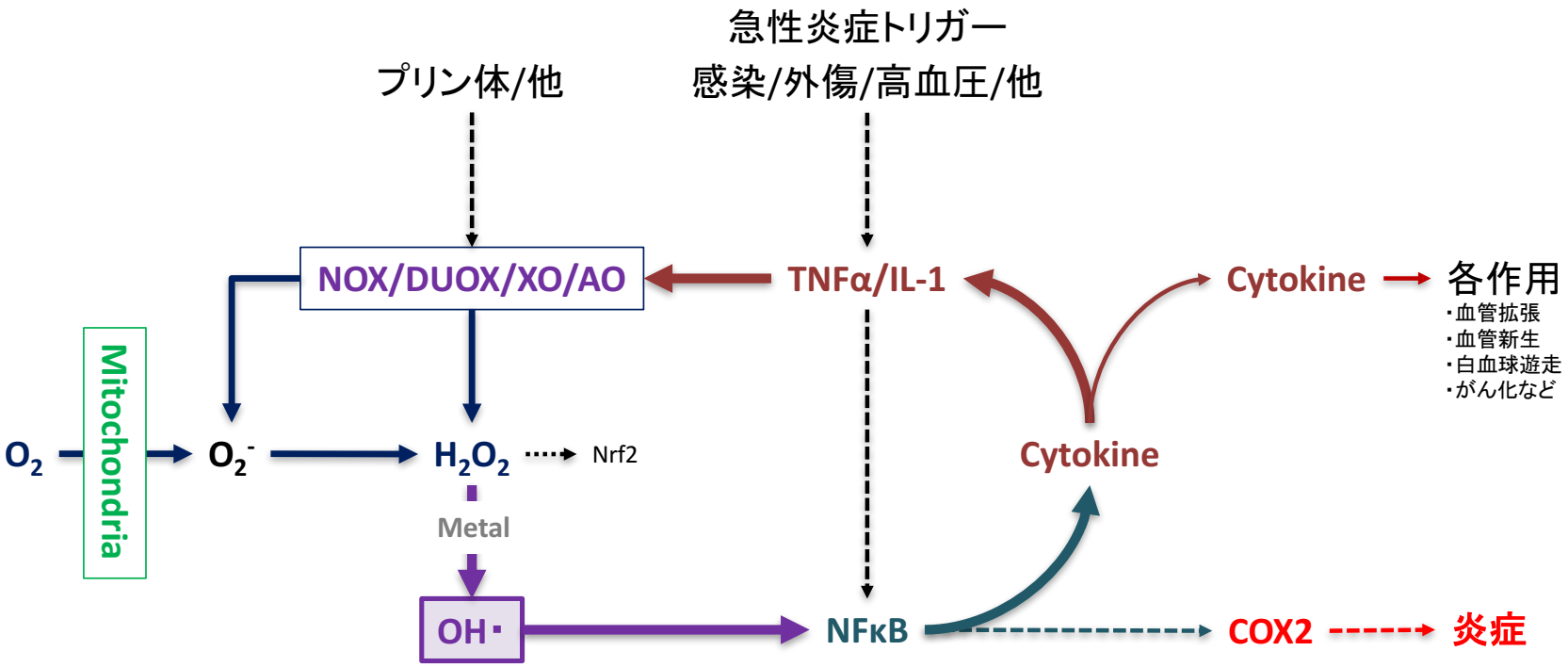
脂肪酸の酸化


O_2
RH
触媒
R・
H_2O
・OH
RH
R・
H_2O
脂質ラジカル
R・
O_2
ROO・
脂質ペルオキシラジカル
（スクワレンペルオキシラジカル）
過酸化脂質
ROOH
Metal
RH
R・
O_2
CYCLE
ROO・
R・
RH
RH
ROOH
ROO・
R・
MDA
ALEs
O_2
ROOH

AGEs合成とROS


糖/果糖/脂肪酸/アミノ酸
シッフ塩基
OH・
RCOs/ALEs
アミノ酸
アマドリ転位物
HbA1c
ROS産生
RAGE結合
AGEs
タンパク糖化劣化
AGEs
サイトカイン産生
糖尿病合併症

サイトカインとROS


急性炎症トリガー
プリン体/他
感染/外傷/高血圧/他
NOX/DUOX/XO/AO
TNFα/IL-1
Cytokine
各作用
・血管拡張
・血管新生
・白血球遊走
・がん化など
Mitochondria
O_2
O_2^-
H_2O_2
Nrf2
Metal
Cytokine
OH・
NFκB
COX2
炎症

臨床の現場

基礎医学から臨床医学へ

臨床水素治療研究会の役割

in vitroの結果 →　in vivoの結果へ
動物実験の結果 → 人間の結果へ

1:安全性の検証
2:効果（投与法、投与量、投与回数）の検証

水素の臨床利用における安全性

1:天然分子である

・安定の最小単位分子
・人間が作った化合物ではない
・天然化合物でもない

2:腸管内で産生される物質である

・消化管内（特に結腸）の**「水素産生菌」によって産生**
・水素産生菌は善玉菌の一種

3:血中に存在する物質である

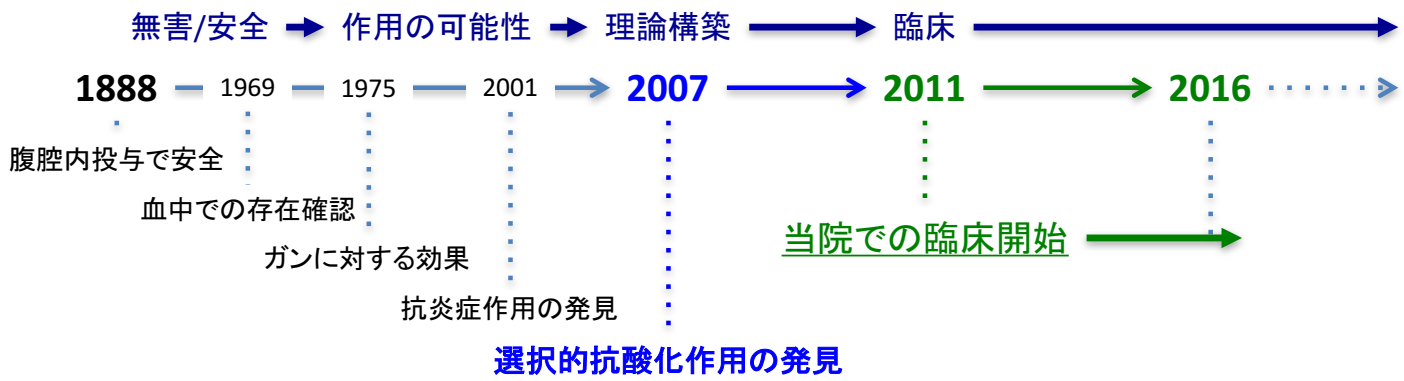
・腸管内で発生した水素ガスが吸収され、**血中に移行**
・肺で換気され、呼気ガスとして放出

4:安全性とともに食品添加物認可

・1995年に食品添加物認可され
・2000年、2004年、2005年、2007年に**継続調査。毒性など認めず**

元来、生体内（血中/体液中）に
存在する物質を投与する治療

水素医学のTimelineと今後の役割



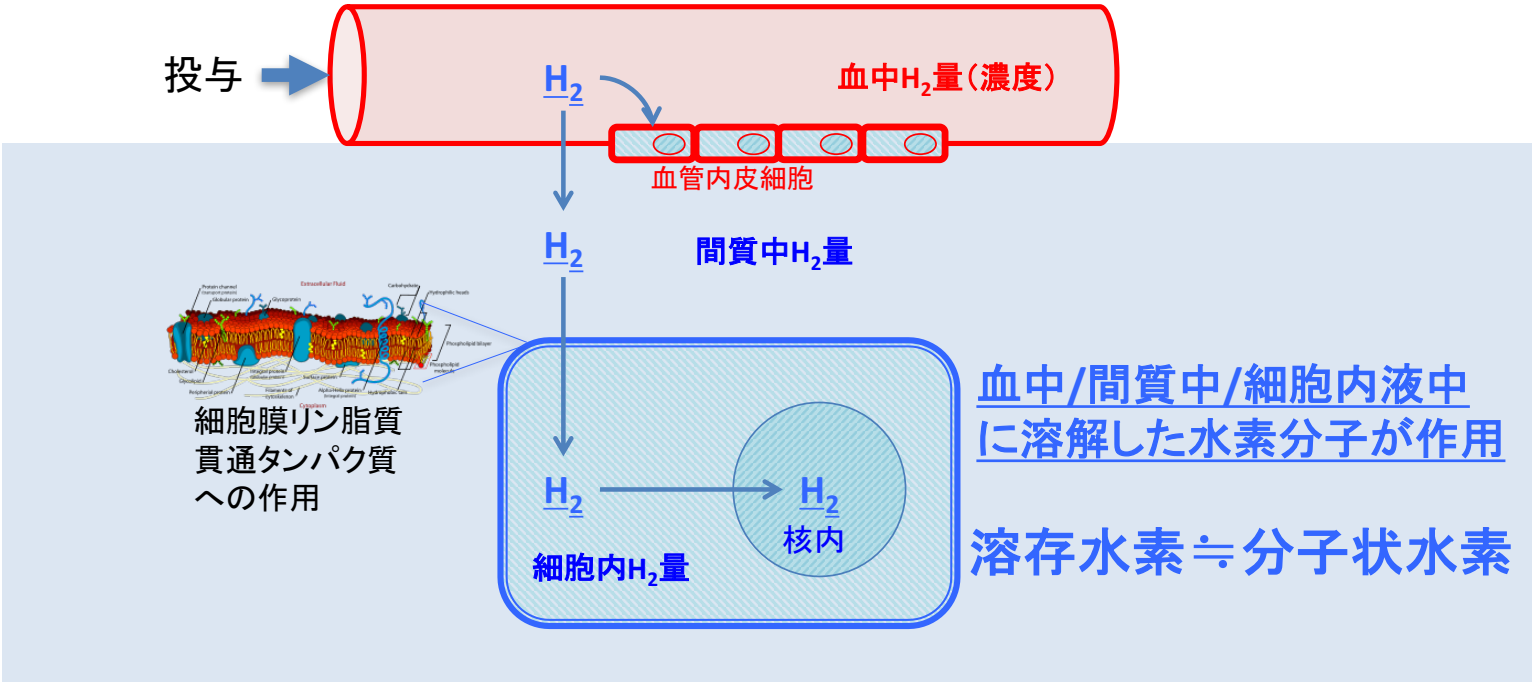
生体に対し毒性はなく
安全に利用でき
各種作用を期待できる

- 延患者数：**1,500人**

<治療内容>

- **水素水点滴**：アンチエジング、予防治療、各種内科系疾患
  疾患では特に糖尿病、高血圧、動脈硬化、神経変性疾患
- **水素注射**：整形外科疾患を中心
  筋肉注射/筋膜間注射/関節内注射
  変形性関節症（膝/股関節）、四十肩/肩こり、腰痛、頸椎症
- **水素発生剤外用（入浴料含）**：皮膚科疾患を中心
- **水素発生剤内服**：[Mg-H_2]
- **水素ガス吸入**：試験中/データ収集中

水素が作用するためには



水素分子が液相（血液,間質液,細胞内液）に溶解する必要がある

過去の論文から考える投与方法の模索

1: 液体に溶解させてから投与

＊水素水（消化管）　＊点滴　＊注射　＊経皮＊

2: 気体を投与し、体内で溶解

＊吸入（肺）　＊経皮＊　＊注入

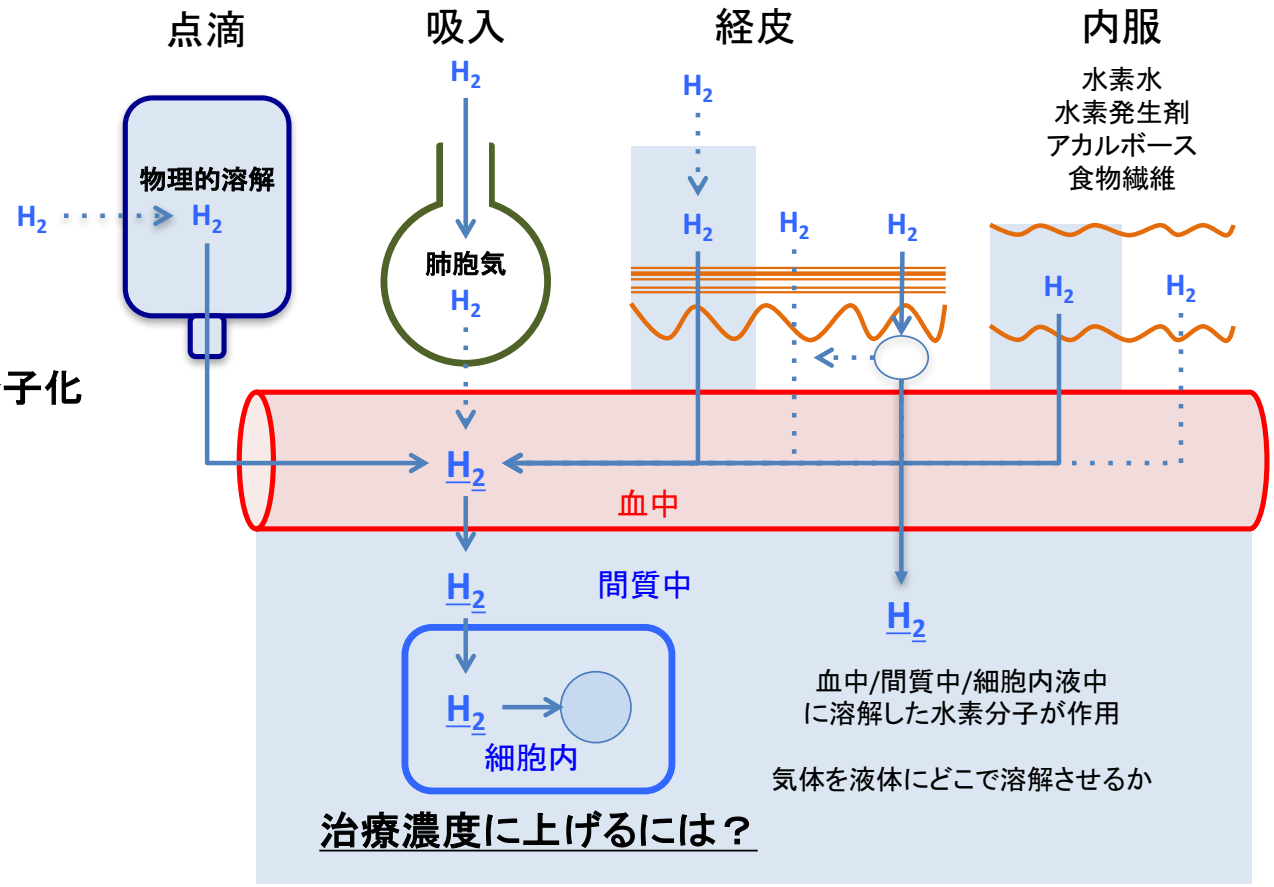
3: 消化管内で発生させ、体内で溶解

＊水素吸蔵体（内服）　＊腸内細菌による発生促進（アカルボースなど）

生体内（細胞内）に分子状水素を供給するには・・・

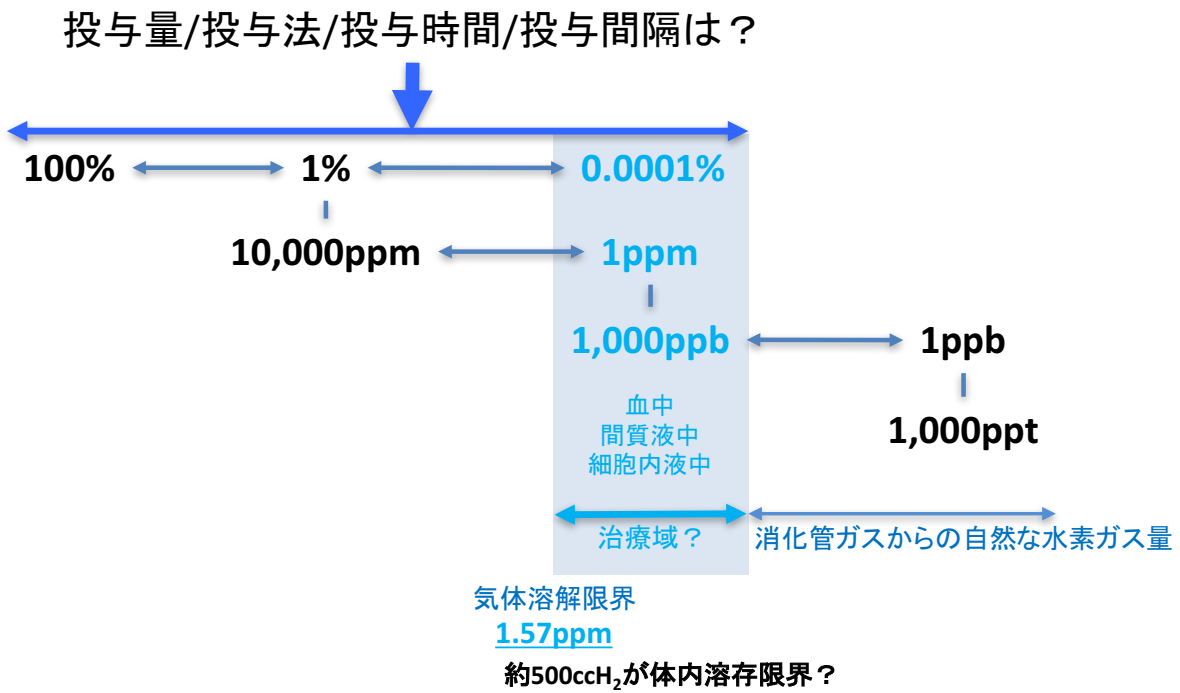
1:気体水素を摂取し、体内で分子化
- 吸入
- ガス注射
- 点滴（ナノバブル）
- 内服（水素発生剤）

2:分子状水素を摂取/注入
- 点滴
- 注射
- 入浴
- 内服（水素水）



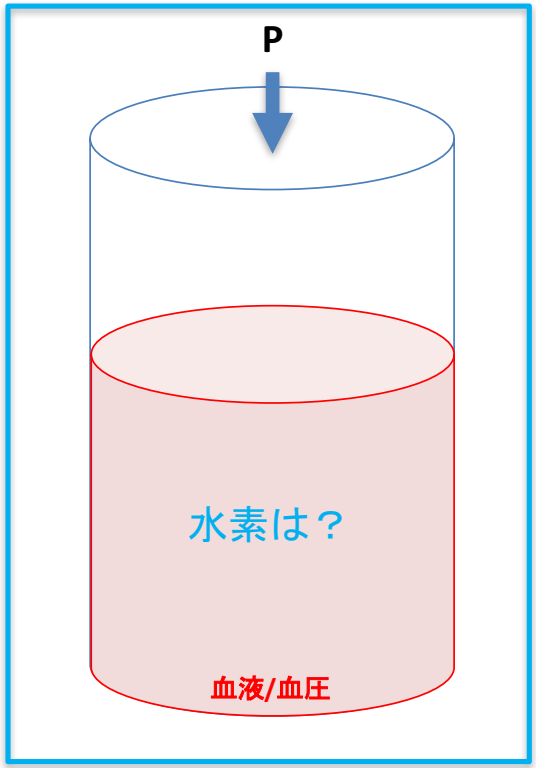
水素量と治療域

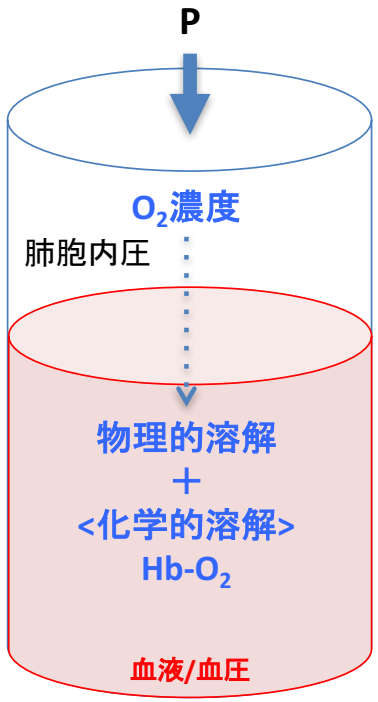
- 水素 (H_2) 分子量2
- 2g/1mol = 2mg/1mmol
- 2g/1mol = 22.4L/1mol
- 1gH_2 = 11.2L
- 1mgH_2 = 11.2cc
- 1ppm ≒ 1mgH_2/1L
- 1ppm ≒ 11.2ccH_2/1L
- 1ppm ≒ 1.12ccH_2/100ml



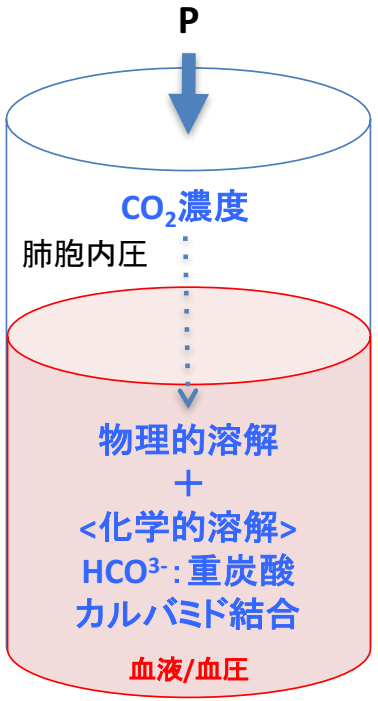
患部{細胞内液 間質液 血液}中の水素濃度限界が作用域と考えられる

生体における気体の溶解



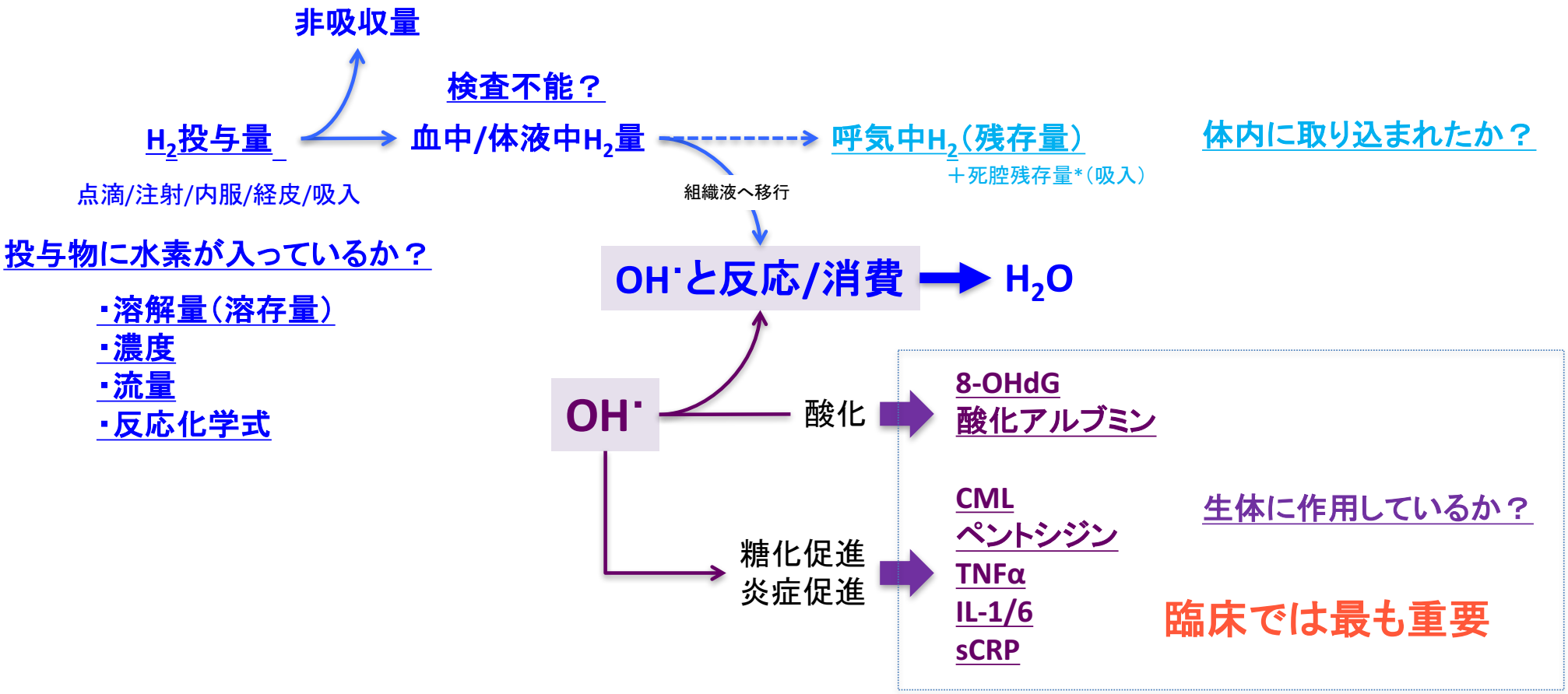


動脈血100mℓ中に20mℓ
物理的溶解は0.3ml
化学的溶解は大部分がヘモグロビンと結合して赤血球内に結合し、酸化ヘモグロビン（HbO2）として存在



動脈血100mℓ中に40～50mℓ
物理的溶解は5％
化学的溶解 80～90％は血漿中に重炭酸塩として存在
5～10％は血漿タンパク質やデオキシヘモグロビンとカルバミノ結合

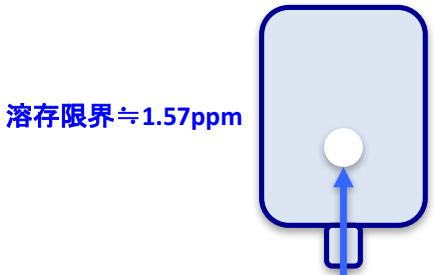
検査の模索


非吸収量
検査不能？
H_2投与量
血中/体液中H_2量
呼気中H_2（残存量）
＋死腔残存量*（吸入）
体内に取り込まれたか？
点滴/注射/内服/経皮/吸入
組織液へ移行
投与物に水素が入っているか？
・溶解量（溶存量）
・濃度
・流量
・反応化学式
$OH^{\cdot}$と反応/消費
H_2O
$OH^{\cdot}$
酸化
8-OHdG
酸化アルブミン
CML
ペントシジン
TNFα
IL-1/6
sCRP
糖化促進
炎症促進
生体に作用しているか？
臨床では最も重要

点滴

点滴/注射溶液
水素化生理食塩水

<生食中への水素溶解>



ヘンリーの法則
ボイル/シャルルの法則
水素ガスの分子間力
液体の分子間力
＋
ナノバブル状態での存在
（ppm計測外）

ボンベ内ガス濃度	: >99.999%
充填ガス濃度	: 99.9999%
湿度	: 0%
充填圧	: 0~100kPa

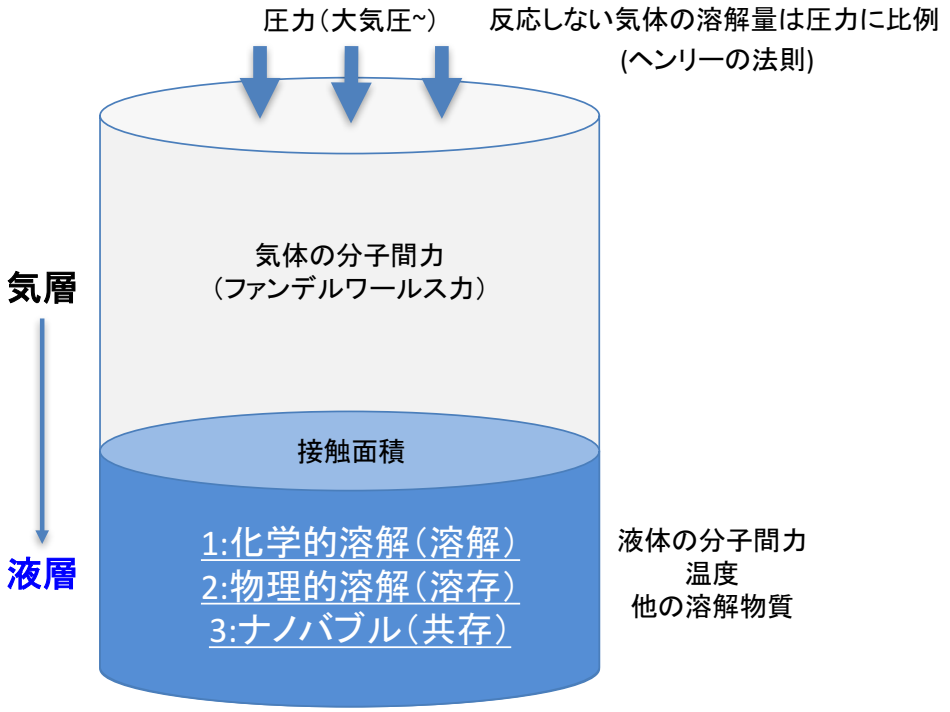
気体水素の液中への侵入

水素の場合

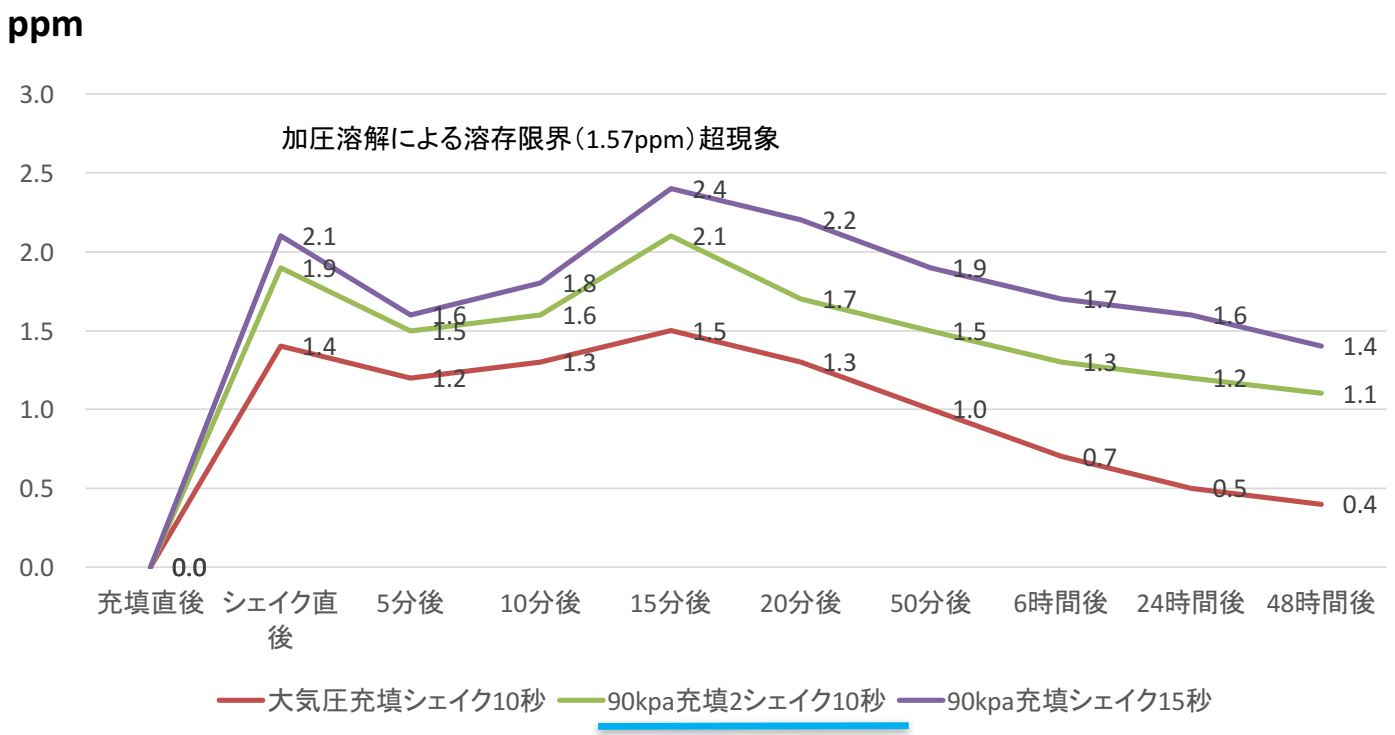
気体状態の水素
（ファンデルワールス力で結合した状態）

↓

分子状水素：上限1.57ppm
＋
ナノバブル（超微細気体）
製造方法による



点滴バッグ内の溶存水素濃度

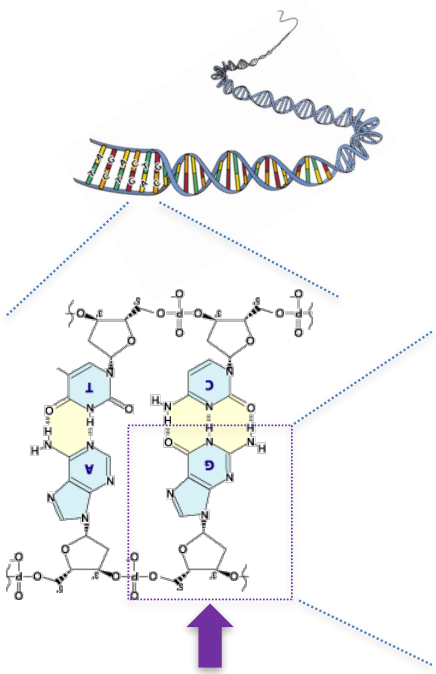


水素点滴

水素ガス注入

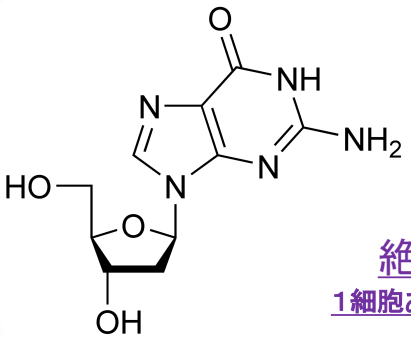
前後にて各種検査を実施

酸化ストレスと8-OHdG



酸化ストレス

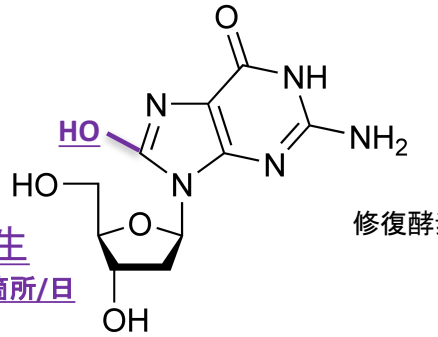
・遺伝子損傷は1細胞あたり**1日5~50万カ所（×60兆個）**
・そのうち、酸化による損傷を検出
・**8-OHdG検査≒遺伝子への酸化ストレススピード**



正常なデオキシグアノジン(dG)

絶えず発生
1細胞あたり数万箇所/日

8-OHdG
8-hydroxy-2'-deoxyguanosine



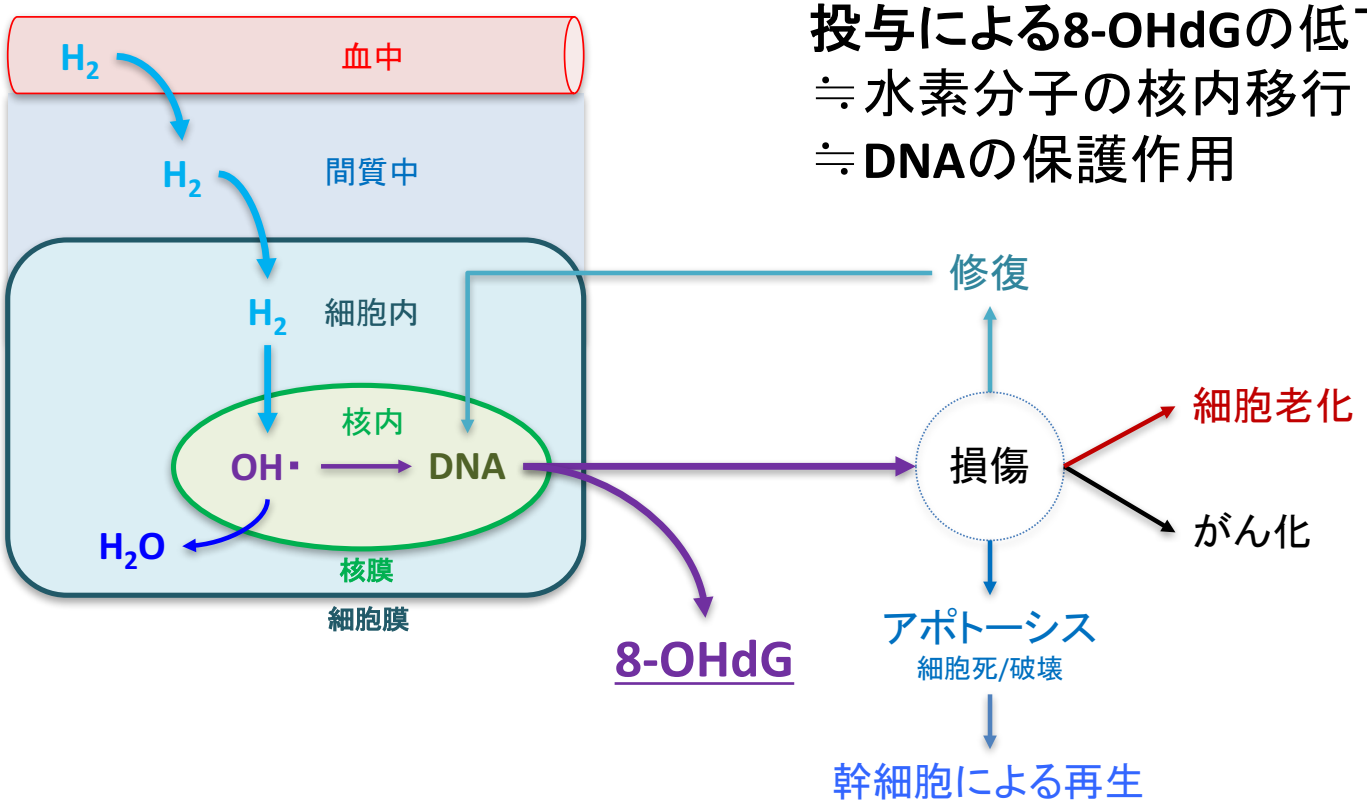
ヒドロキシ化（酸化損傷）

修復酵素による排除

尿中

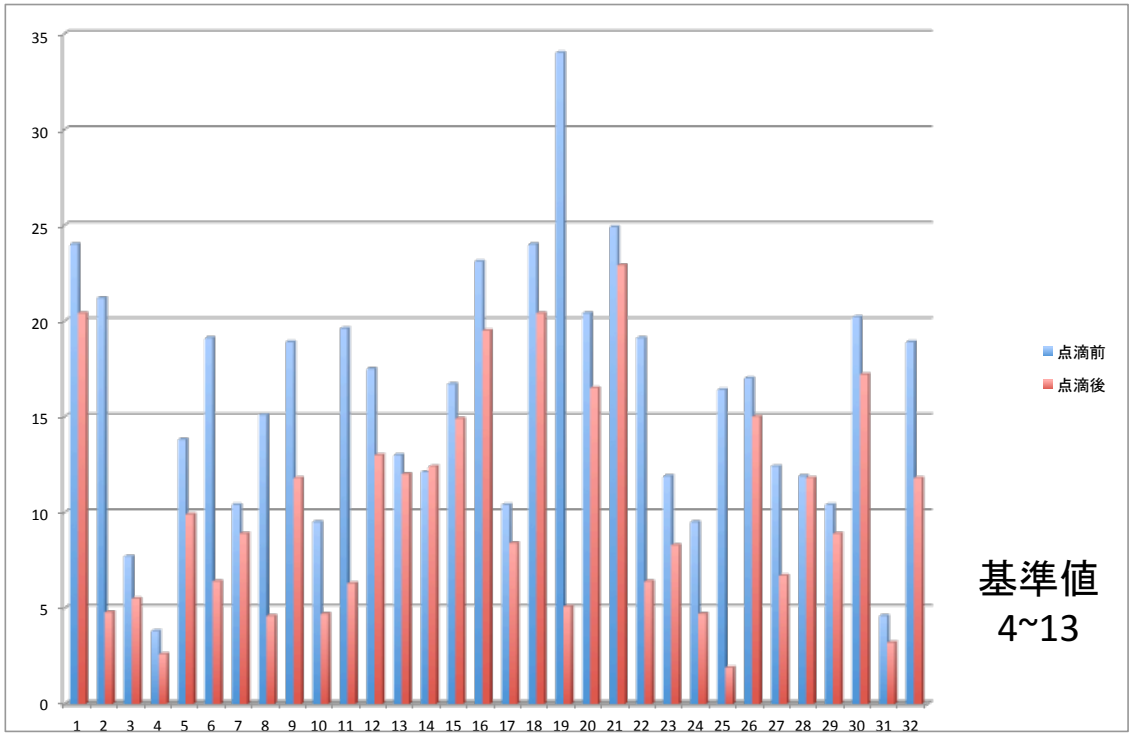
4つのデオキシリボースのうちデオキシグアノジンの酸化産物

投与と8-OHdGの関係



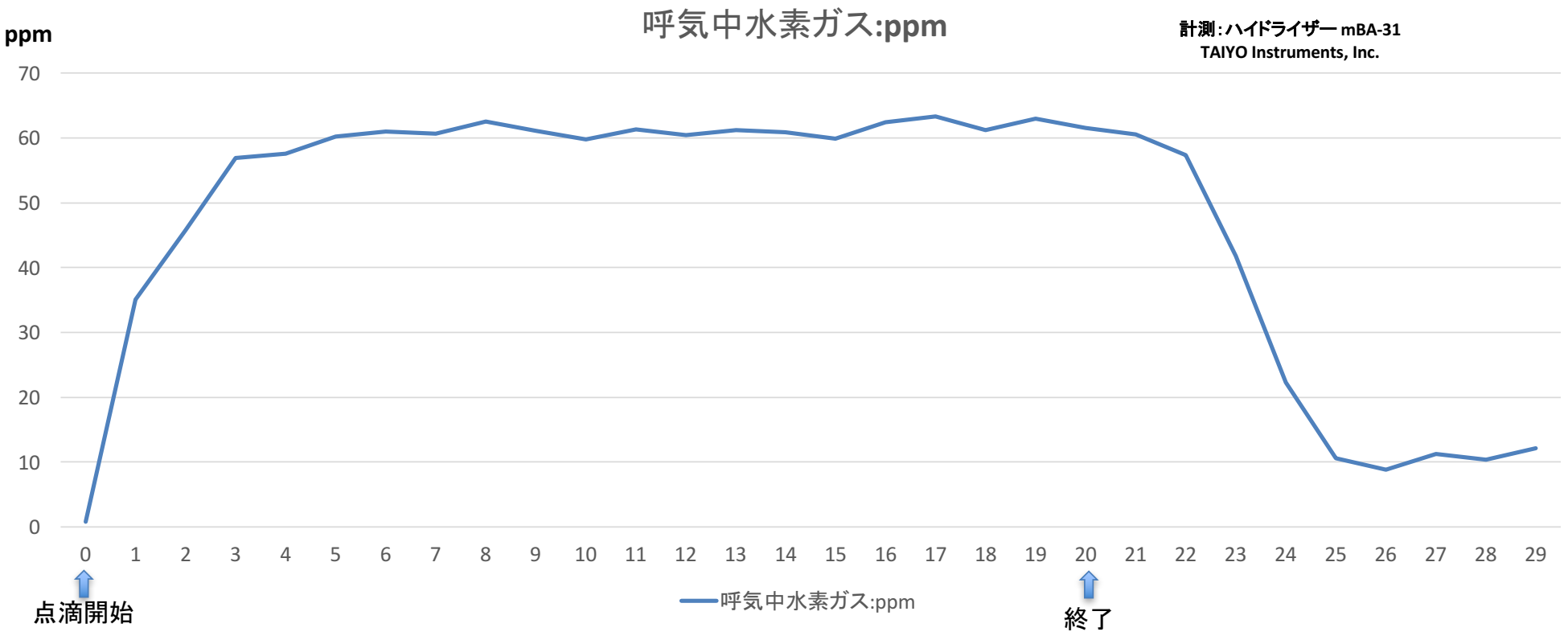
投与による8-OHdGの低下
≒水素分子の核内移行
≒DNAの保護作用

水素化生理食塩水点滴による8-OHdGの変化



・ほぼすべての症例において、8-OHdGの低下を認める
・DNAの酸化損傷スピードにブレーキをかけた

水素生理食塩水の点滴による経時的呼気水素ガス濃度変化

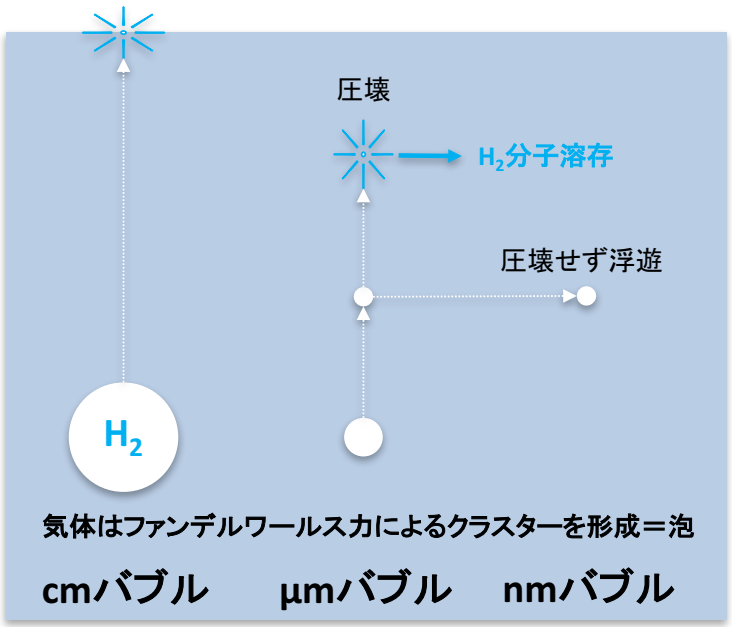


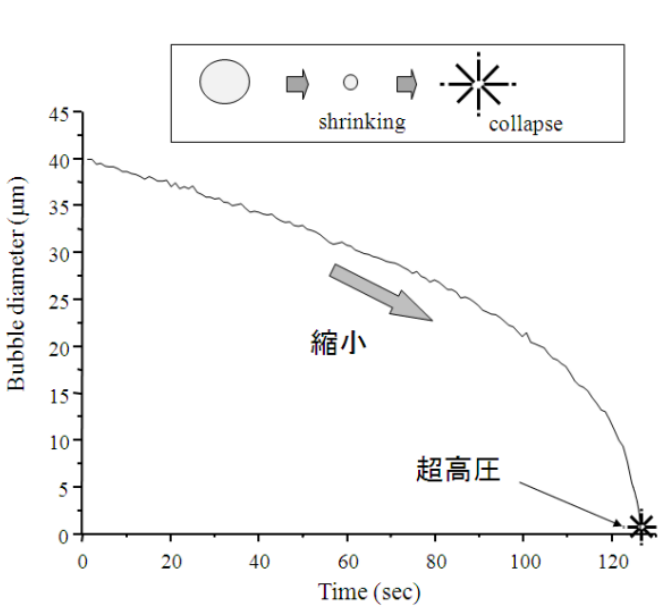
点滴中　呼気ガス内に高濃度の水素ガスを検出
溶存水素量（**2.4ppm　100cc**）から考えて多すぎる

水素ナノバブルの検証

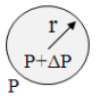
マイクロ/ナノバブルの発生

水面で破裂





Young-Laplace equation

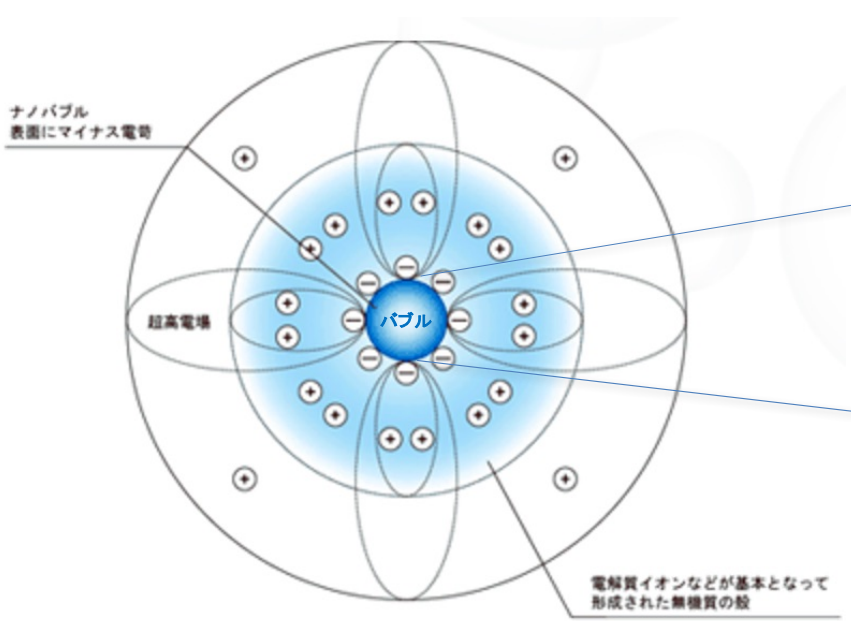


$\Delta P = 2\sigma / r$

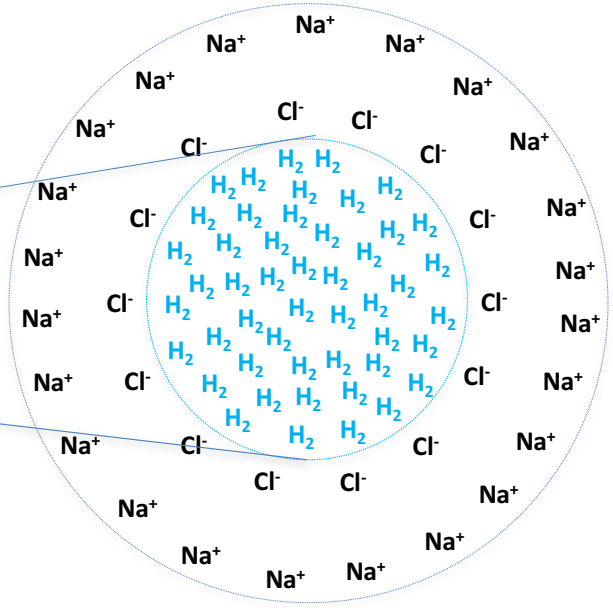
Diameter μm	ΔP kg/cm2
10	0.3
1	3
0.1	30
|	|
0	∞

		（50μm）	（<100nm）
水中浮上速度	25cm/秒	2mm/秒	0.008μm/秒
1m上昇の時間	3~5秒	約10分	1~4年

生食（電解質含有水）内のナノバブル



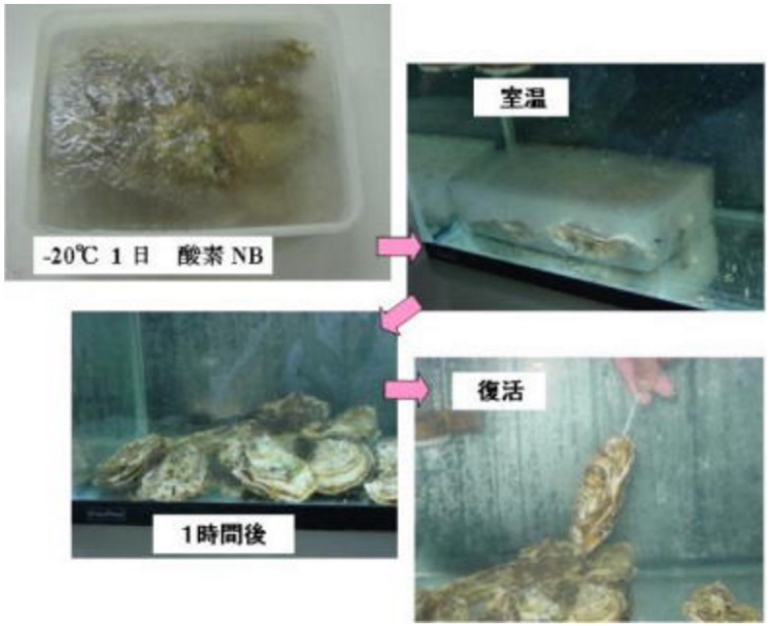
Na^+ と Cl^- によるイオン殻



内部は高圧100%水素ガス
含まれる分子数の計測は不可能

ナノバブルの作用

【淡水魚／海水魚の共存実験】
成長促進
感染症の改善



【冷凍牡蠣の再生実験】
細胞保護能力

医療におけるナノバブル研究

1. オゾンナノバブルにおける研究

（1）東京医科歯科大学

・細菌、ウイルス等の微生物に起因する様々な疾病の治療又は予防に好適な組織の殺菌と消毒用製剤に関する研究
①歯周病の治療及び予防用製剤等の研究
②口内炎等の治療及び予防剤等組織修復又は組織再生用製剤の研究

（2）順天堂大学
・東京医科歯科大学との共同研究
・オゾンナノバブルの耐性菌等の殺菌・消毒の研究

（3）新潟大学
・オゾンナノバブルによる殺菌及び消毒の研究
手術における手指等の消毒

（4）東京都健康安全研究センター・微生物部ウイルス研究科
・オゾンナノバブルのノロウイルスの不活化の研究
・オゾンナノバブルのエアロゾル化と圧力の研究
・噴霧による感染ウイルスの不活化

2. 酸素ナノバブルにおける研究

（1）自治医科大学（循環器内科）
・動脈硬化性の病気に関するナノバブル水の抑制効果
・腎硬化等臓器への保護作用効果
・酸素ナノバブルの抗炎症作用について…

（2）東京医科歯科大学(病院)
・心臓等の臓器への保存液の検証
・組織細胞の修復再生等の研究
・組織の滅菌・消毒液としての検証
・生体ならびに組織のおける上記の滅菌・保存・修復・再生に関する応用研究の統括

3. その他

・組織保存能の研究
・殺菌機能の研究
・組織修復能の研究（褥瘡改善）
・再生機能の研究
・IGF-1分泌促進作用の研究
・ホメオスターシス維持機能の研究

医学におけるナノバブル研究も始まったばかり

動脈硬化性の病気に関するナノバブル水の抑制効果 - 自治医科大学　循環器内科/医学博士　北條行弘

動脈硬化による心筋梗塞、脳梗塞などの病気はいまや日本人の主要な死因です。75歳以上の高齢者は脳や心臓の動脈の慢性疾患をかかえていることが多く、生活をおくる上で大きな問題となっています。日本はますます高齢化社会を迎えることになり、健やかに老いることは近い将来の大きな問題です。

我々（自治医科大学　医学博士　北條）はこうした動脈硬化性の病気をナノバブル水が抑えることができるかどうかを研究してきました。酸素ナノバブル水を使った実験で

（1）動脈の内側を覆う内皮細胞の炎症を抑え
（2）活性化した白血球が内皮に付着すること阻害することが明らかになり、
（3）その作用は従来考えられてきたメカニズムとはまったく異なったものではないか考えられ、この結果を日本循環器学会で発表しました。

健康な内皮細胞を保つことは動脈硬化を予防する上で非常に重要なことであり、この実験結果は酸素ナノバブル水が今までにない動脈硬化予防の可能性を秘めたものであることを示されました。

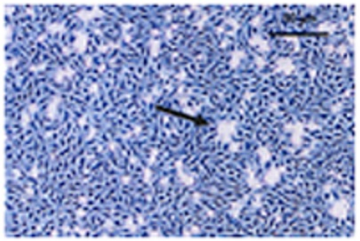
さらに内皮の外側にある筋肉細胞（平滑筋細胞）の過剰な増殖を抑えることも確認できました。ラットの実験では腎臓のように小さな血管の集合体をもつ臓器を保護する結果も得られています。

酸素ナノバブル水はすでに訪れつつある高齢化社会において、高齢者の健康を維持し、良好な生活の質を保つ大きな役目を果たす可能性があり、今後その機序のさらなる解明や循環器疾患以外の各医療分野での応用が期待されます。

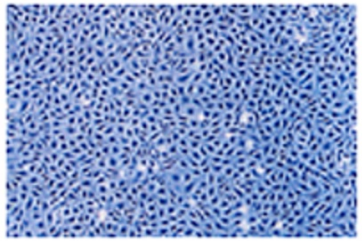
【参考:発表資料】

酸素ナノバブルは活性化したマクロファージの内皮細胞への接着を抑制します。

矢印：活性化したマクロファージが内皮に密着している様子
をしめします。



コントロール



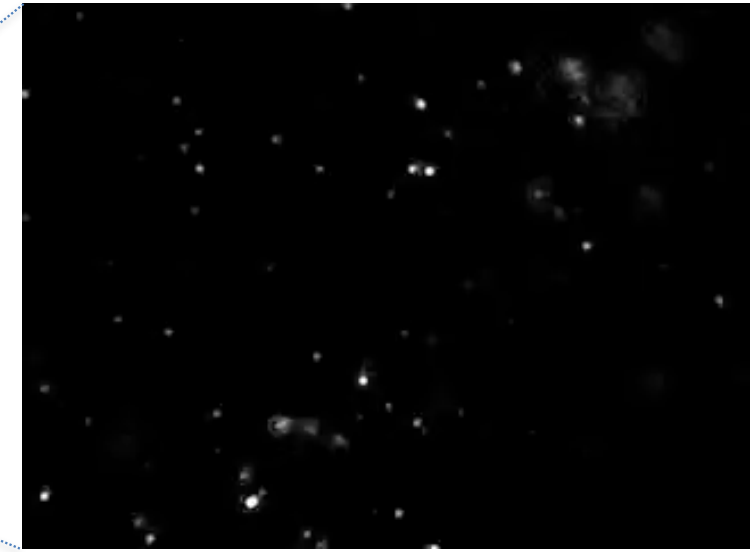
酸素ナノバブルで処理した内皮細胞

2006年　日本循環器学会

マイクロスコープ下での水素ナノバブルの存在

目視はできない

コロイド（ナノバブル）の帯電によるブラウン運動

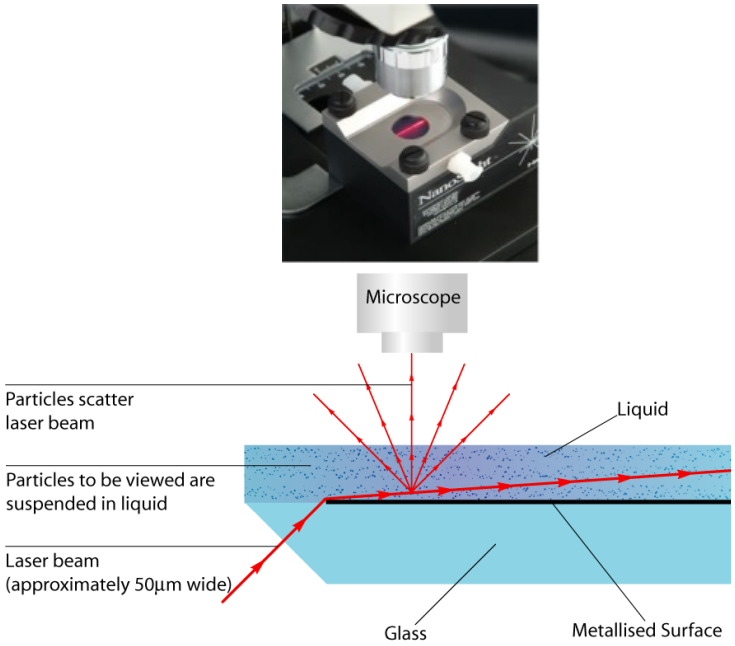


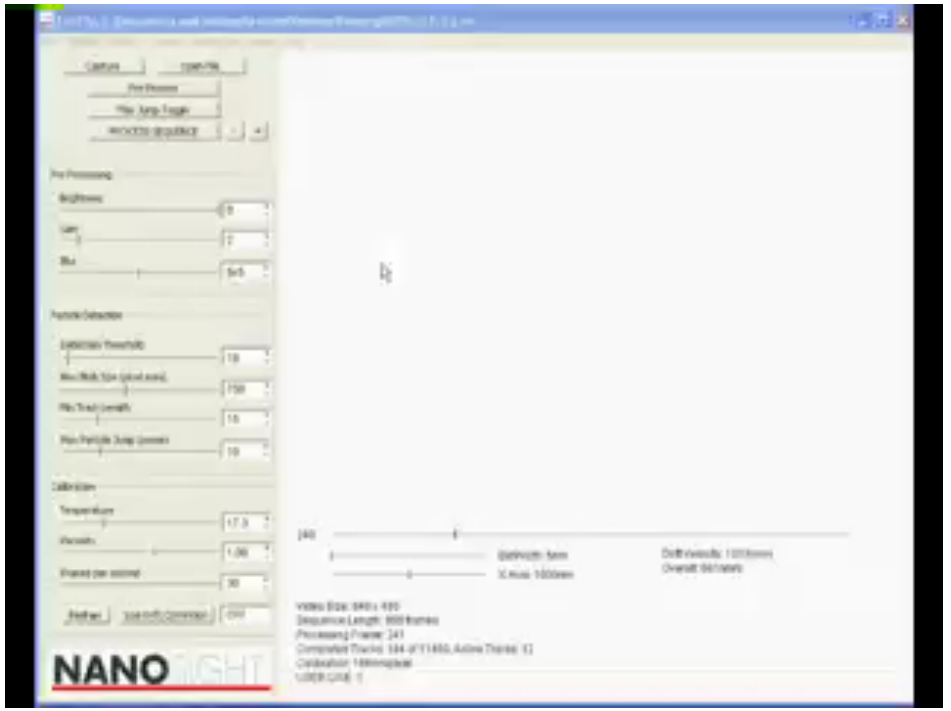
ストークス・アインシュタインの式： $\langle x,y\rangle^2 = \dfrac{K_B T t_s}{3\pi\eta d_h}$

粒子が小さいほどブラウン運動が激しい

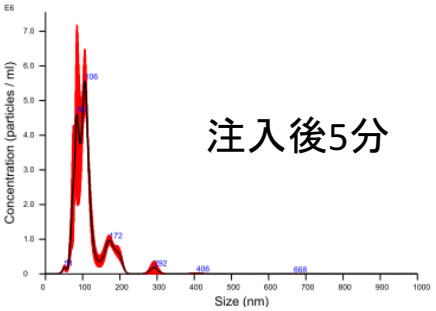
点滴バッグ内のナノバブル計測

NanoSight

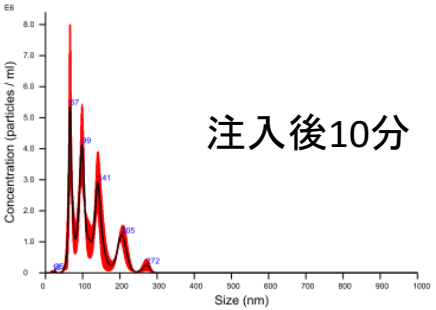




点滴バッグ中のナノバブル:1　バブル径

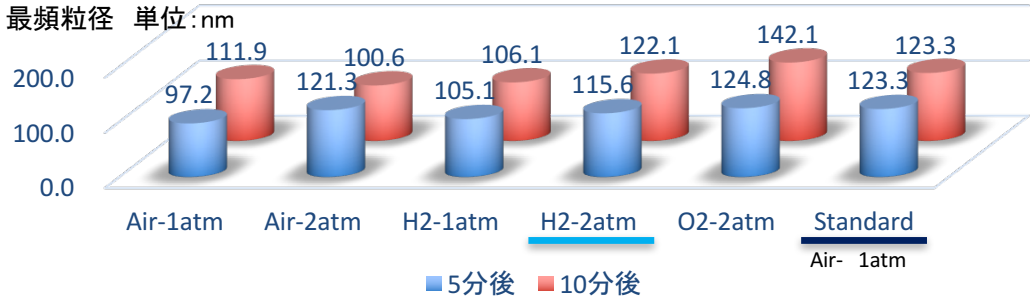


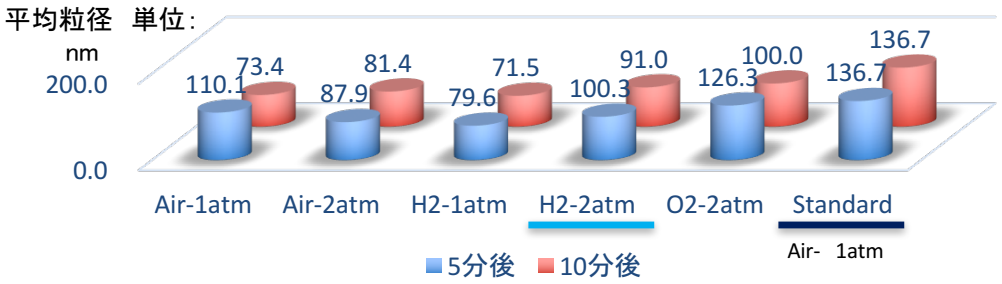
注入後5分



注入後10分

H_2-2atm

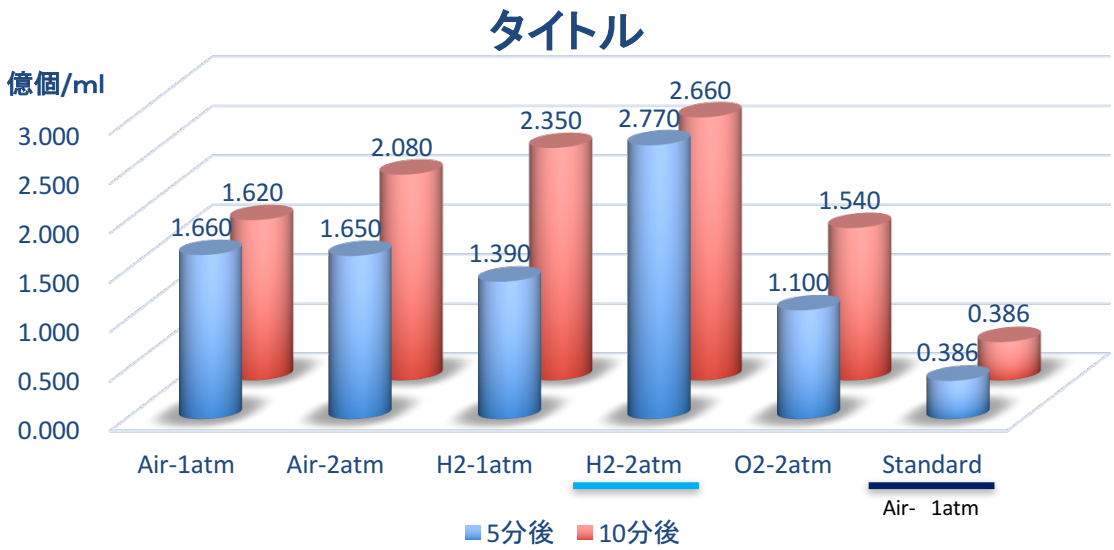




・すべて最小毛細血管径（**8~10μm**）を超えない
・水素ガスによるバブル径は酸素より小さい

1μm = 1,000nm

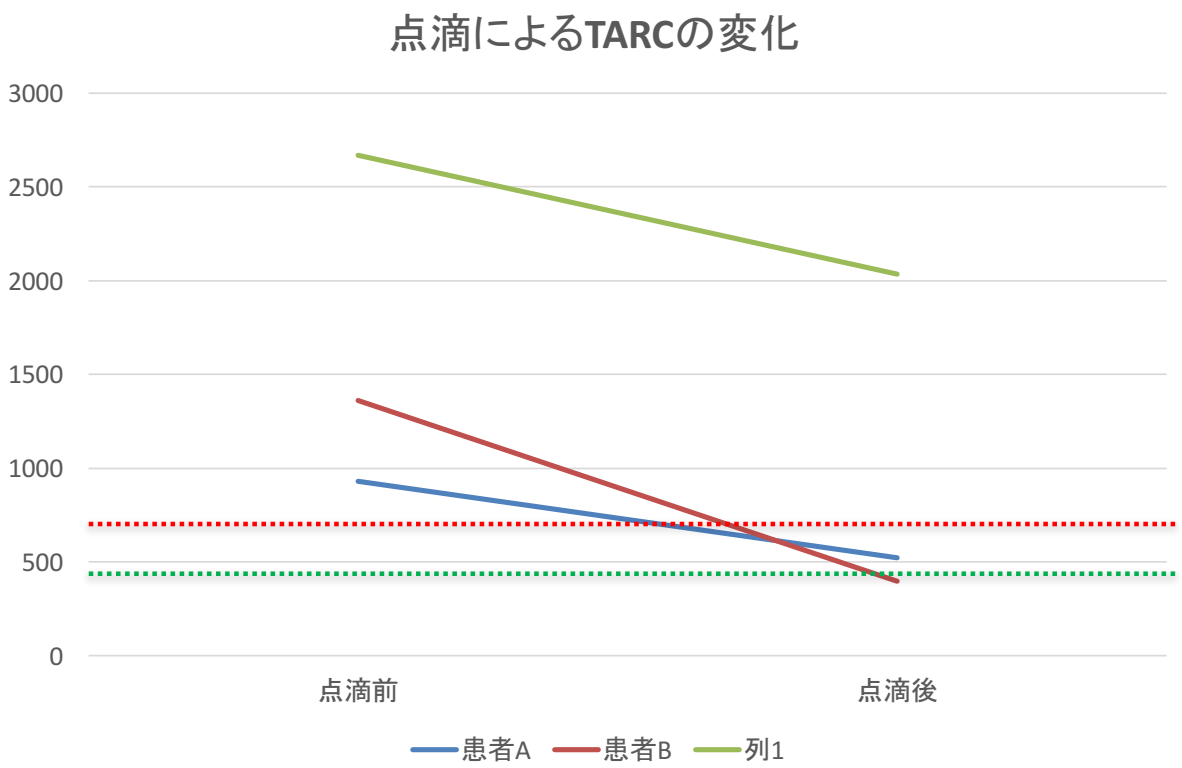
点滴バッグ中のナノバブル:2　バブル量



・通常点滴バッグにもバブルは存在
→以前より<u>ナノバブルは投与されていた</u>
・水素ナノバブルは発生が多い
・バブル量は分子の大きさに比例

・**約2億8000個/ml**のナノバブルの存在を確認
・通常点滴バッグ内にも**3900万個/ml**のナノバブルが存在（<u>点滴していた</u>）
・**280億個/100ml, 700億個/250ml**のバブルを点滴
・バブル内（超高圧圧縮バブル内）は100%水素ガス（100万ppm）
・点滴による水素分子の投与量は天文学的数字となる

点滴によるTARCの変化

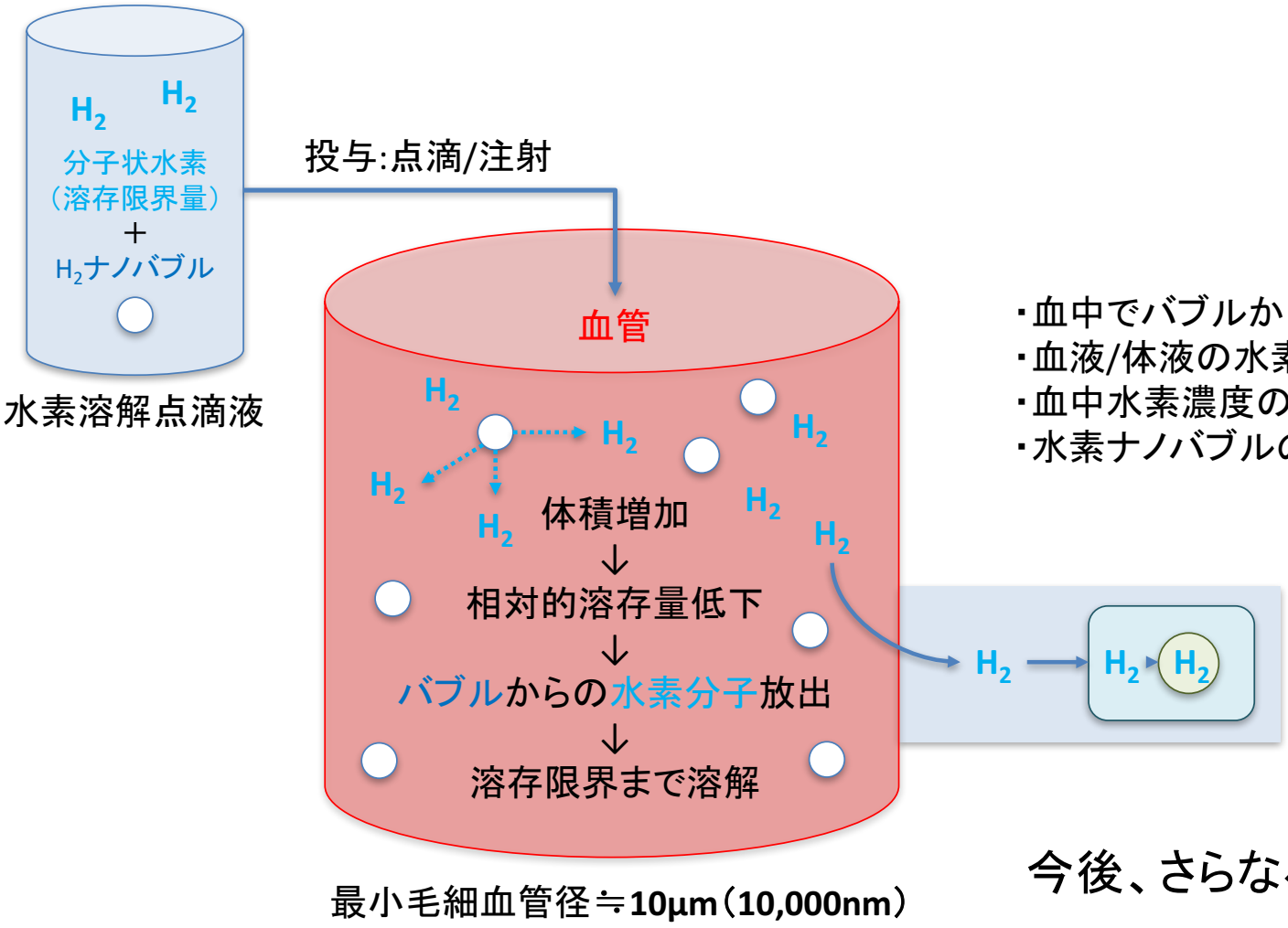


TARC(Thymus and activation-regulated chmokine)
白血球走化作用を持つケモカインの一種で、過剰産生されるとTh2細胞を病変局所に引き寄せ、IgE抗体の産生や好酸球の活性化が起こり、アレルギー炎症反応を惹起すると考えられている。
アトピー性皮膚炎において特異性がみられ、重症になるほど著明に上昇し、軽快に伴い減少する。

<450pg/ml :正常
450~700pg/ml :軽症
>700pg/ml :中等度以上

現在、データ蓄積中

水素ナノバブル仮説

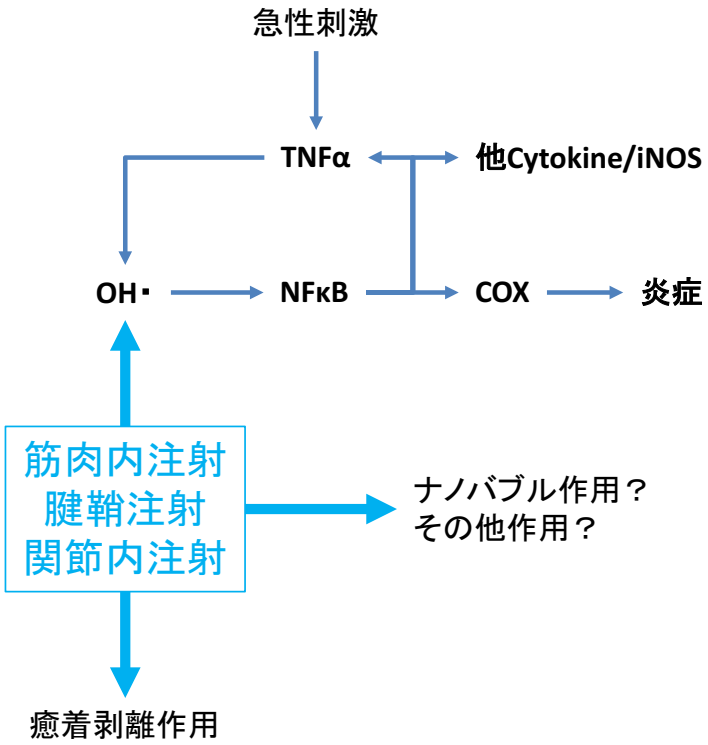


・血中でバブルからの水素放出？
・血液/体液の水素分子溶存量は？
・血中水素濃度の計測は可能か？
・水素ナノバブルの作用の可能性

今後、さらなる検証を重ねる予定

注射

水素（ナノバブル）生食注射とその可能性



生理食塩水の作用

・トリガーポイントの鎮痛作用機序として以前から研究
・筋膜性疼痛症候群(MPS)研究会で疼痛緩和に利用
・生理食塩水による筋膜剥離が鎮痛作用
・鎮痛効果は水素（バブル）水のほうが強い

溶存水素（水素分子）の作用

・水素のNFκB抑制作用？

水素ナノバブルの作用

・バブル内気体の種類によって作用が違う
・水素ナノバブルの発表はない
・ナノバブルの抗炎症作用？その他作用？
・未知の作用の可能性

関節内注射の検討

- 肩関節周囲炎
- 変形性膝関節症
- 慢性関節リウマチ
- 股関節臼蓋形成不全
- 足関節捻挫後遺症
- 顎関節症

に対する関節内注射

加齢変化
アスリート
膠原病
外傷後　　など

疼痛の軽減
稼働時/歩行時痛の軽減
関節腫脹の軽減
可動域の拡大

を認める

内服

種類

水素水

- 分子状水素を含ませた水
- 『水素』として摂取
- 投与できる水素分子量が少ない
- **1.5ppm**上限として**11.5cc/ℓ**の水素摂取
- 不安定で抜けやすい

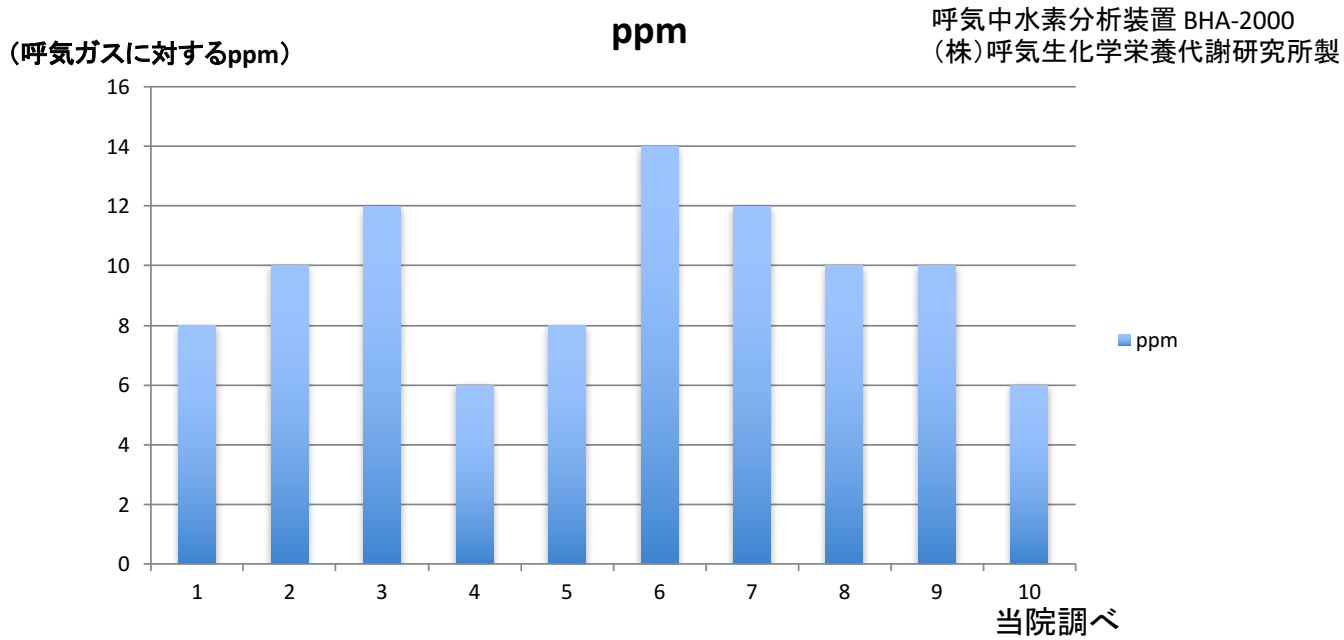
水素吸蔵体

- 体内で分子状水素を発生させる物質
- **MgH_2**、フラナガン、珊瑚カルシウムなどが存在
- <gあたりの発生量>が明確なのは**MgH_2**
- **発生理論（化学式）が明確はのはMgH_2**
- **<時間あたりの発生量>は不明（変動）**
- **食品未認可のためMgH_2は『研究用試薬』として処方**

糖質吸収遅延剤

- 腸内細菌による水素ガス発生を促す
- アカルボースによる論文が存在
- 腸内細菌量/種類によって発生量が違う

安静時の呼気中水素濃度



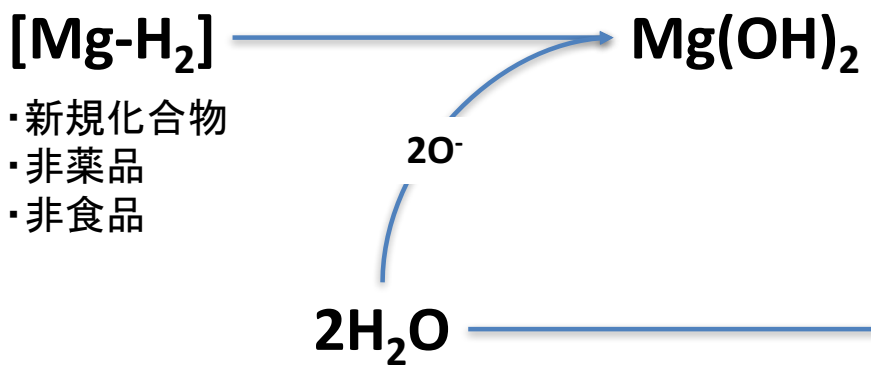
大気中水素ガスは『**0.5ppm**』と考えられているため、この呼気中水素ガスは、消化管内（腸内細菌）および体内（細胞）で産生されたものと考えられる

摂取内容/摂取時間などで発生量は大きく変動

アカルボースによる水素ガス発生は現在データ収集中

水素吸蔵合金

臨床水素治療研究会では「Substance H_2」と命名し、臨床用試薬として使用

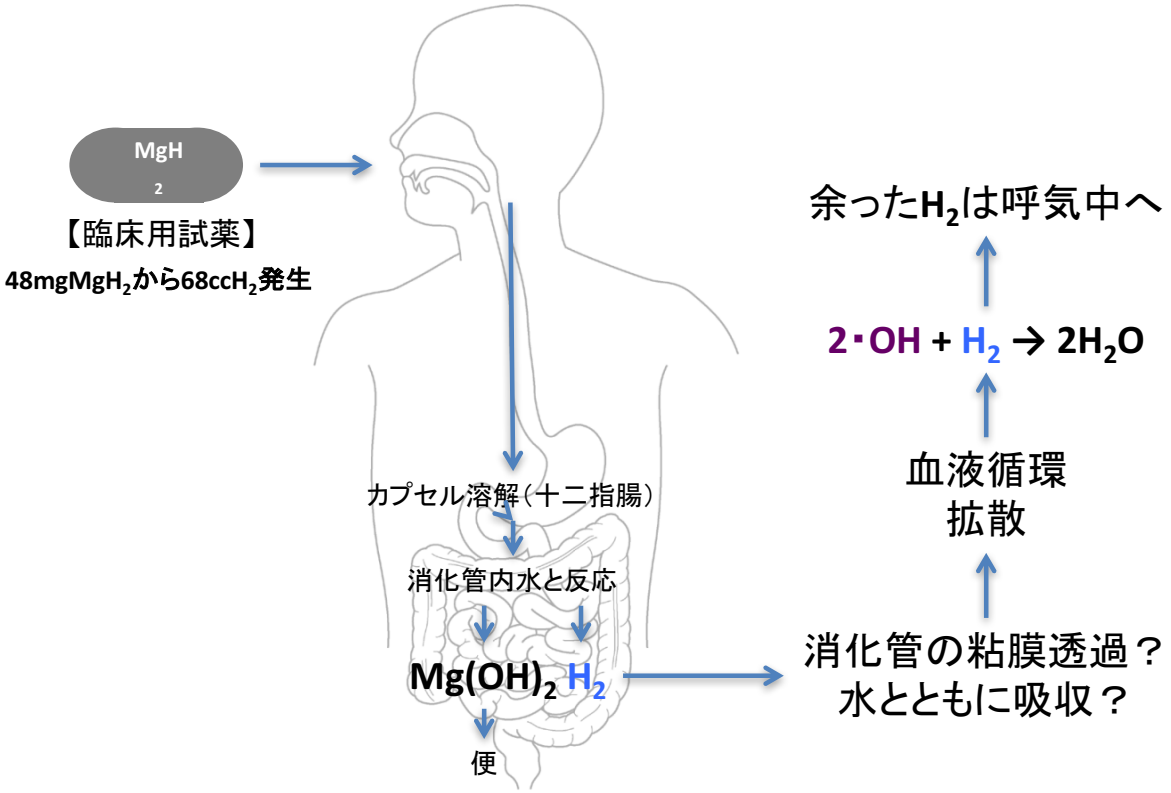


1g[Mg-H_2] → 1.7L H_2

1g H_2 = 11.2L H_2

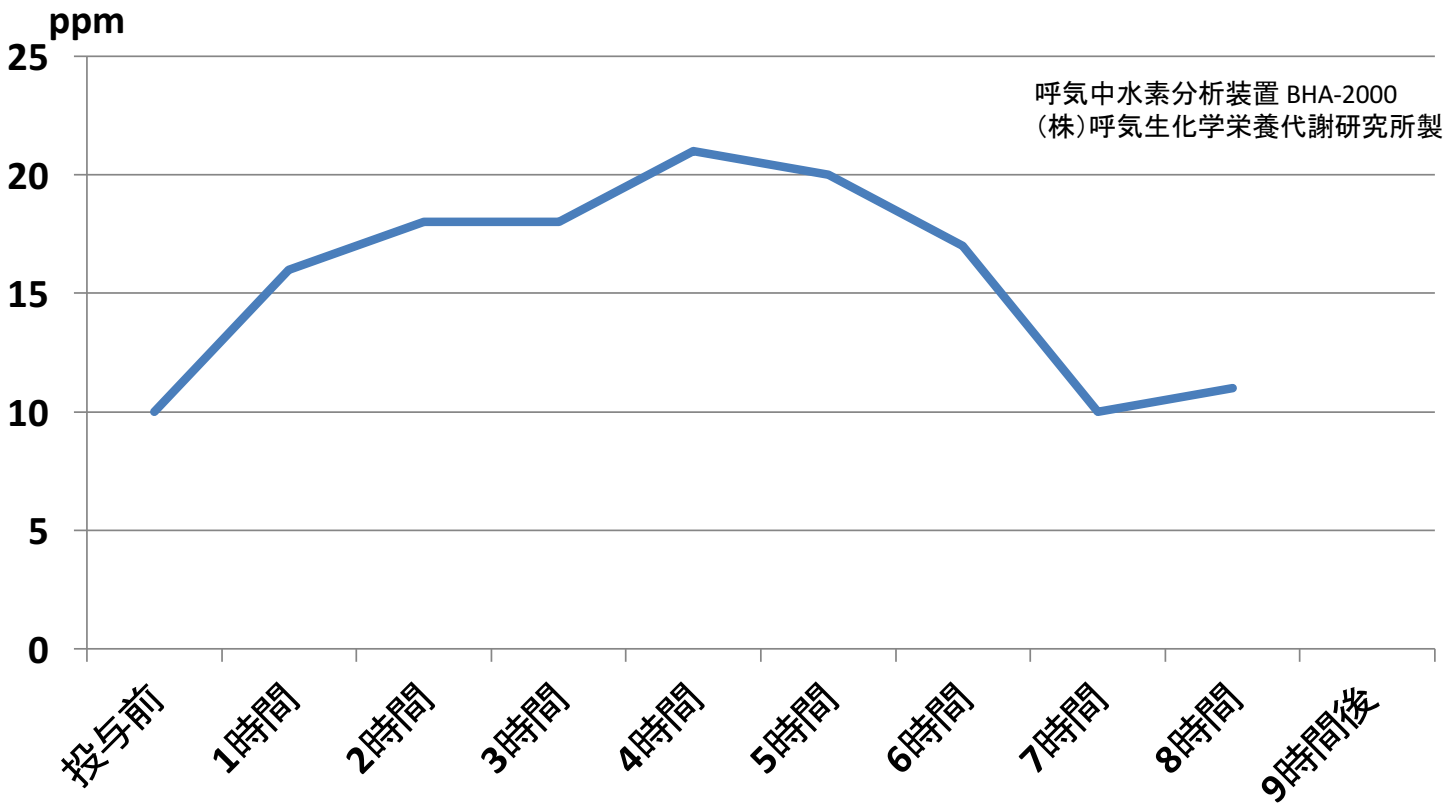
Mg吸蔵体カプセルによる投与

$MgH_2 + 2H_2O \rightarrow Mg(OH)_2 + 2H_2$



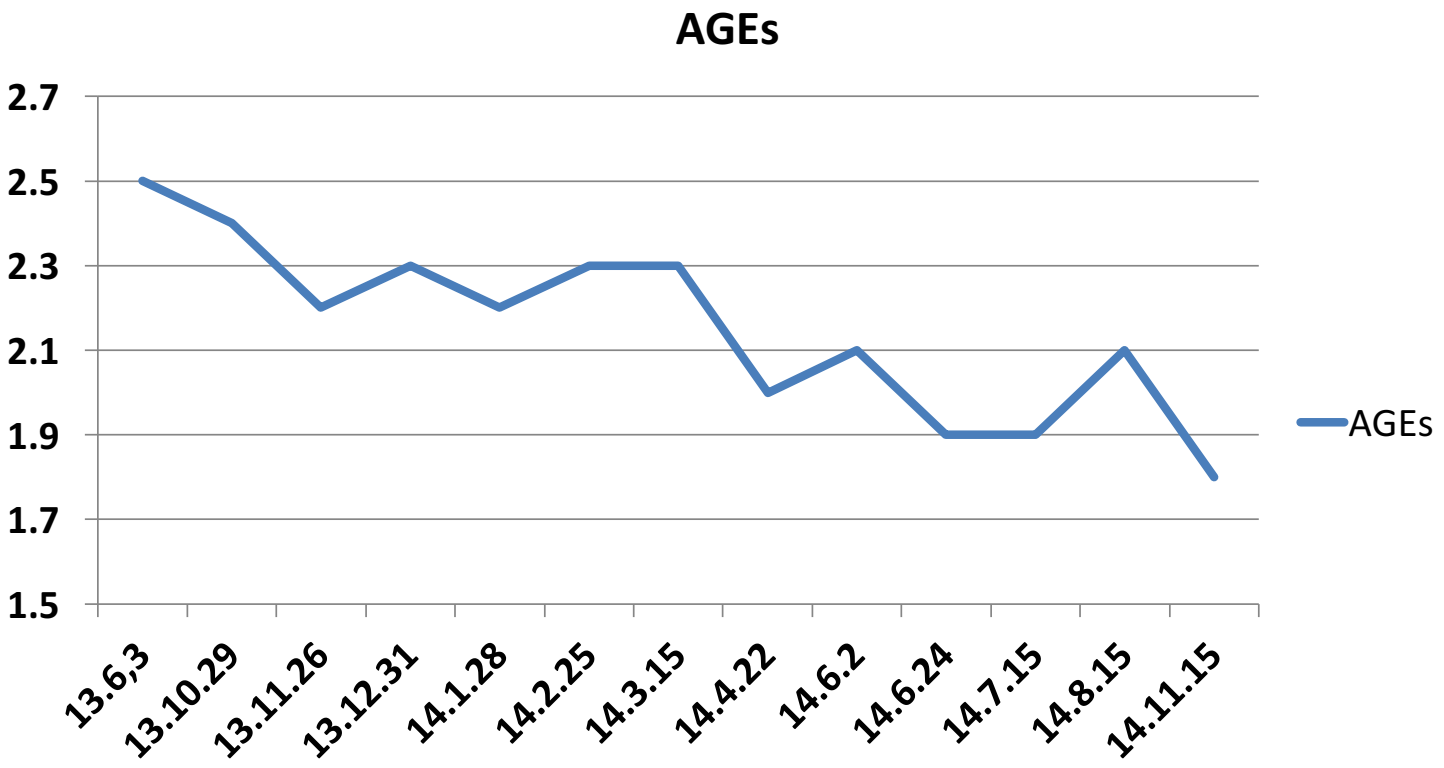
腸内細菌が水素ガスを発生する状態を再現

内服による呼気中H_2ガスの変化



2012年当院調べデータ

長期内服による皮下AGEsの変化



内服２

腸内細菌を利用した水素ガス発生と利用

1969: 腸内細菌が水素を産生し血中へ移行

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ORIGINAL ARTICLE ARCHIVE

Production and Excretion of Hydrogen Gas in Man

Michael D. Levitt, M.D.

N Engl J Med 1969; 281:122-127 | July 17, 1969 | DOI: 10.1056/NEJM196907172810303

Share:

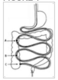
Abstract

Technics employing intestinal infusions of gas were used to study H_2 production in the human intestine. The volume of H_2 in the bowel of 10 normal subjects varied from 0.06 to 29 ml. H_2 production, which averaged 0.24 ml per minute in the fasting state, sharply increased after intestinal instillation of lactose to a mean peak rate of 1.6 ml per minute. Ingestion of food also increased H_2 production by seven-fold to 30-fold. In the normal intestine, more than 99 per cent of H_2 production was colonic, but small-bowel production was increased in a patient with excessive numbers of small-bowel bacteria. H_2 production in man is primarily dependent upon the delivery of ingested, fermentable substrates to an abundant intestinal flora that normally is present only in the colon.

A mean of 14 per cent of the total H_2 production was excreted by the lungs, and rates of breath H_2 excretion and H_2 production correlated well (r = 0.94). Respiratory H_2 excretion can therefore be used as an indicator of intestinal H_2 production.

MEDIA IN THIS ARTICLE

FIGURE 1



Schematic Representation of the Position of the Triple-

ARTICLE ACTIVITY

206 articles have cited this article

2004: アカルボースが心筋リスクを軽減

Eur Heart J. 2004 Jan;25(1):10-6.

Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies.

Hanefeld M[1], Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M.

Author information

Abstract

AIMS: To assess if treatment with the alpha-glucosidase inhibitor acarbose can reduce cardiovascular events in type 2 diabetic patients.

METHODS AND RESULTS: This meta-analysis included seven randomized, double-blind, placebo-controlled acarbose studies with a minimum treatment duration of 52 weeks. Type 2 diabetic patients valid for safety were randomized to either acarbose (n=1248) or placebo (n=932). The primary outcome measure was the time to develop a cardiovascular event. Primary analysis was conducted using Cox regression analysis. The effect of acarbose on metabolic parameters was also investigated. Acarbose therapy showed favourable trends towards risk reduction for all selected cardiovascular event categories. The treatment significantly reduced the risk for "myocardial infarction" (hazards ratio=0.36 [95% CI 0.16-0.80], P=0.0120) and "any cardiovascular event" (0.65 [95% CI 0.48-0.88], P=0.0061). Glycaemic control, triglyceride levels, body weight and systolic blood pressure also improved significantly during acarbose treatment.

CONCLUSION: Intervention with acarbose can prevent myocardial infarction and cardiovascular disease in type 2 diabetic patients while most of them are already on intensive concomitant cardiovascular medication.

Comment in

No evidence for a reduction of myocardial infarctions by acarbose. [Eur Heart J. 2004]

PMID: 14683737 [PubMed - indexed for MEDLINE] Free full text

腸内細菌が消化管内で発生する水素も
実は効果（作用）を発揮していた
体内発生水素の減少による弊害
水素治療≒欠乏水素量の補充療法？

2009: アカルボースがヒドロキシラジカルの生成を抑制

J Cardiovasc Pharmacol. 2009 Jul;54(1):25-30. doi: 10.1097/FJC.0b013e3181a98b53.

Acarbose reduces myocardial infarct size by preventing postprandial hyperglycemia and hydroxyl radical production and opening mitochondrial KATP channels in rabbits.

Minatoguchi S[1], Zhang Z, Bao N, Kobayashi H, Yasuda S, Iwasa M, Sumi S, Kawamura I, Yamada Y, Nishigaki K, Takemura G, Fujiwara T, Fujiwara H.

Author information

Abstract

BACKGROUND: Acarbose, an antidiabetic drug, is an alpha-glucosidase inhibitor that can inhibit glucose absorption in the intestine. A recent large-scale clinical trial, STOP-NIDDM, showed that acarbose reduces the risk of myocardial infarction. We examined whether acarbose reduces myocardial infarct size and investigated its mechanisms.

METHODS AND RESULTS: Rabbits were fed with 1 of 2 diets in this study: normal chow, 30 mg acarbose per 100 g chow for 7 days. Rabbits were assigned randomly to 1 of 4 groups: control (n = 10), acarbose (n = 10), acarbose + 5HD (n = 10, intravenous 5 mg/kg of 5-hydroxydecanoate), and 5HD (n = 10, intravenous 5 mg/kg of 5HD). Rabbits then underwent 30 minutes of coronary occlusion followed by 48-hour reperfusion. Postprandial blood glucose levels were higher in the control group than in the acarbose group. The infarct size as a percentage of the left ventricular area at risk was reduced significantly in the acarbose (19.4% +/- 2.3%) compared with the control groups (42.8% +/- 5.4%). The infarct size-reducing effect of acarbose was abolished by 5HD (43.4% +/- 4.7%). Myocardial interstitial 2,5-dihydroxybenzoic acid levels, an indicator of hydroxyl radicals, increased during reperfusion after 30 minutes of ischemia, but this increase was inhibited in the acarbose group. This was reversed by 5HD.

CONCLUSION: Acarbose reduces myocardial infarct size by opening mitochondrial KATP channels, which may be related to the prevention of postprandial hyperglycemia and hydroxyl radical production.

PMID: 19487955 [PubMed - indexed for MEDLINE]

2015:アカルボースによる水素が炎症を抑制

Eur J Pharmacol. 2015 Sep 5;762:96-101. doi: 10.1016/j.ejphar.2015.04.051. Epub 2015 May 9.

Hydrogen gas production is associated with reduced interleukin-1β mRNA in peripheral blood after a single dose of acarbose in Japanese type 2 diabetic patients.

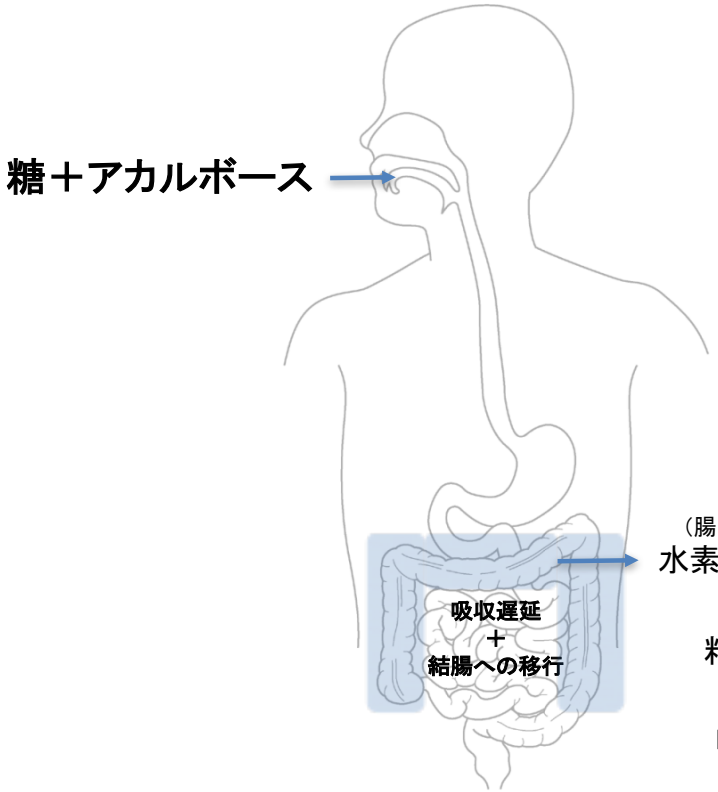
Tamasawa A[1], Mochizuki K[2], Hariya N[3], Saito M[1], Ishida H[1], Doguchi S[1], Yanagiya S[4], Osonoi T[5].

Author information

Abstract

Acarbose, an α-glucosidase inhibitor, leads to the production of hydrogen gas, which reduces oxidative stress. In this study, we examined the effects of a single dose of acarbose immediately before a test meal on postprandial hydrogen gas in breath and peripheral blood interleukin (IL)-1β mRNA expression in Japanese type 2 diabetic patients. Sixteen Japanese patients (14 men, 2 women) participated in this study. The mean±standard deviation age, hemoglobin A1c and body mass index were 52.1±15.4 years, 10.2±2.0%, and 27.1±6.0kg/m(2), respectively. The patients were admitted into our hospital for 2 days and underwent test meals at breakfast without (day 1) or with acarbose (day 2). We performed continuous glucose monitoring and measured hydrogen gas levels in breath, and peripheral blood IL-1β mRNA levels before (0min) and after the test meal (hydrogen gas: 60, 120, 180, and 300min; IL-1β: 180min). The induction of hydrogen gas production and the reduction in peripheral blood IL-1β mRNA after the test meal were not significant between days 1 (without acarbose) and 2 (with acarbose). However, the changes in total hydrogen gas production from day 1 to day 2 were closely and inversely associated with the changes in peripheral blood IL-1β mRNA levels. Our results suggest that an increase in hydrogen gas production is inversely associated with a reduction of the peripheral blood IL-1β mRNA level after a single dose of acarbose in Japanese type 2 diabetic patients.

体内発生水素（分子状水素）の体内移行と作用

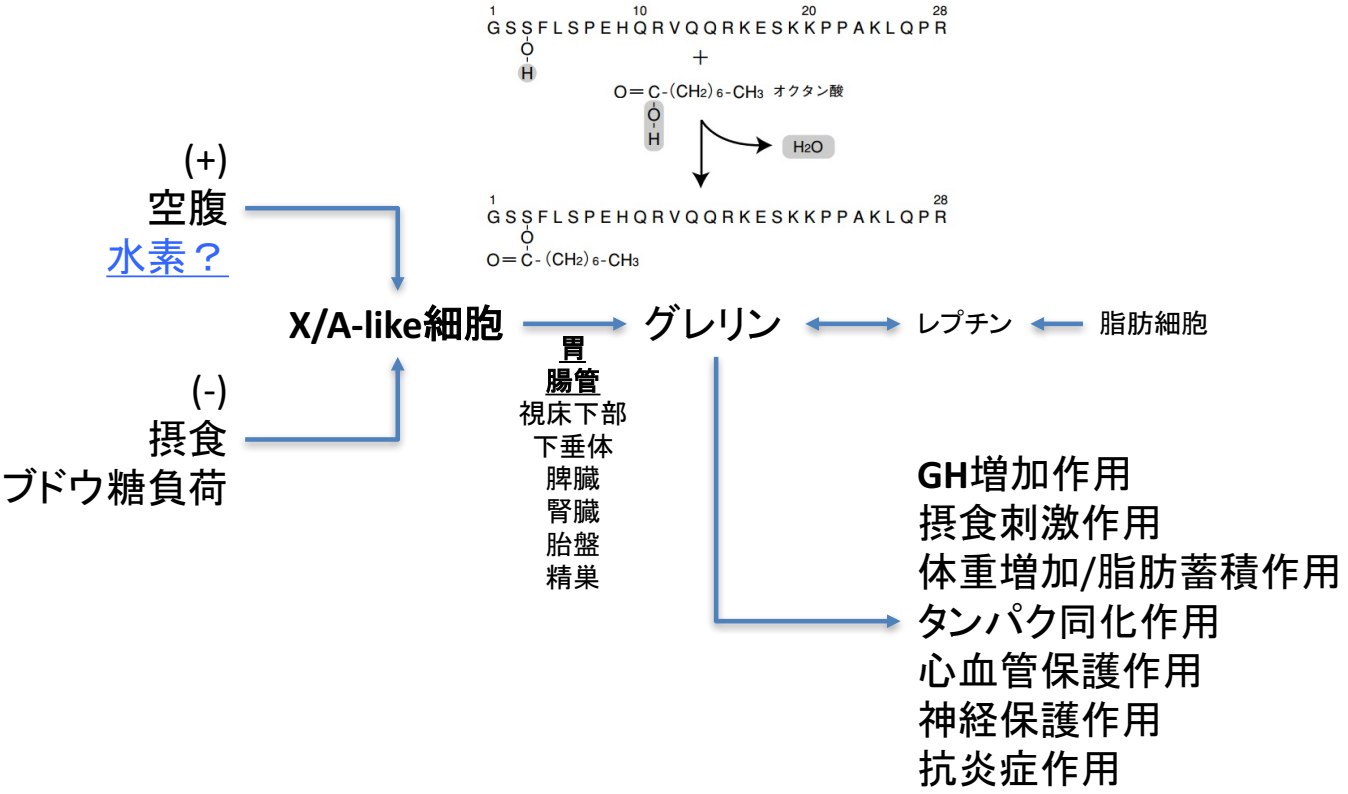


（腸内細菌）
水素生産菌による水素ガスの発生(1969)

粘膜からの吸収と血中移行(1969) → 各種作用 2004 2009 2015

呼気ガス/放屁による排泄(1969)

水素（水）とグレリン分泌

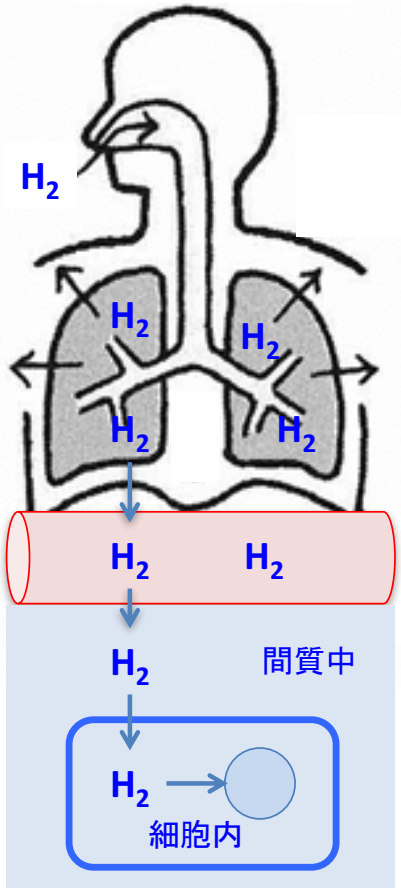

1 10 20 28
G S S F L S P E H Q R V Q Q R K E S K K P P A K L Q P R
O
H
+
O＝C-(CH2)6-CH3 オクタン酸
O
H
H2O
1 28
G S S F L S P E H Q R V Q Q R K E S K K P P A K L Q P R
O
O＝C-(CH2)6-CH3
(+)
空腹
水素？
(-)
摂食
ブドウ糖負荷
X/A-like細胞
胃
腸管
視床下部
下垂体
脾臓
腎臓
胎盤
精巣
グレリン
レプチン
脂肪細胞
GH増加作用
摂食刺激作用
体重増加/脂肪蓄積作用
タンパク同化作用
心血管保護作用
神経保護作用
抗炎症作用

気体の投与

ガス吸入と注入

吸入

吸入水素ガスの肺胞→血管移行



吸入H_2濃度　:1～60%（O_2:21%は必要）
温度（体温）　:37℃
吸入圧　:1～α（CPAP/陽圧呼吸など）
接触面積　:肺胞面積 約70m^2

↓

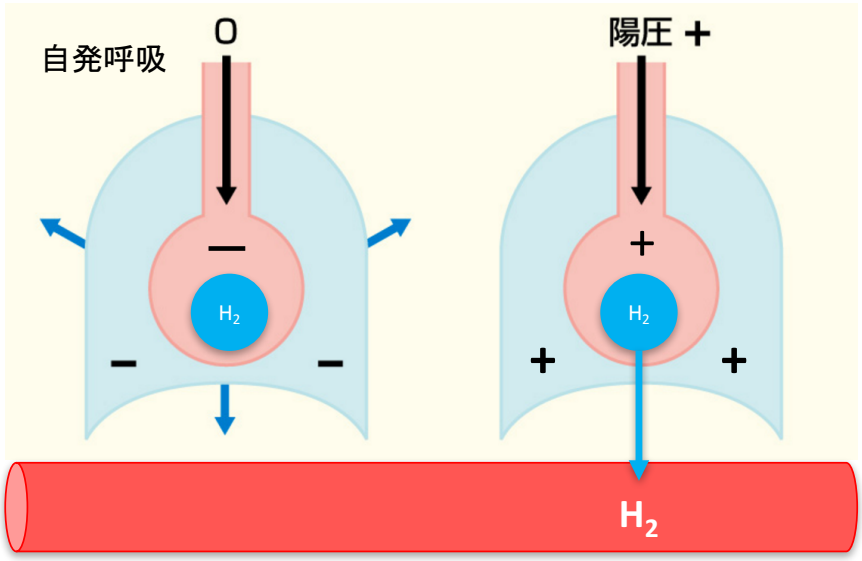
血中/間質液中/細胞内液中H_2濃度
飽和限界は？
限界に達するまでの時間は？

体内液量

体重の60%
細胞内液:40%
組織液」15%
血漿・リンパ液:4.5%
体腔液:0.5%

ヘンリーの法則と吸入水素の溶解

ヘンリーの法則：気体の溶解量は圧力に比例
≒陰圧時に溶解しない　　陽圧呼吸で溶解

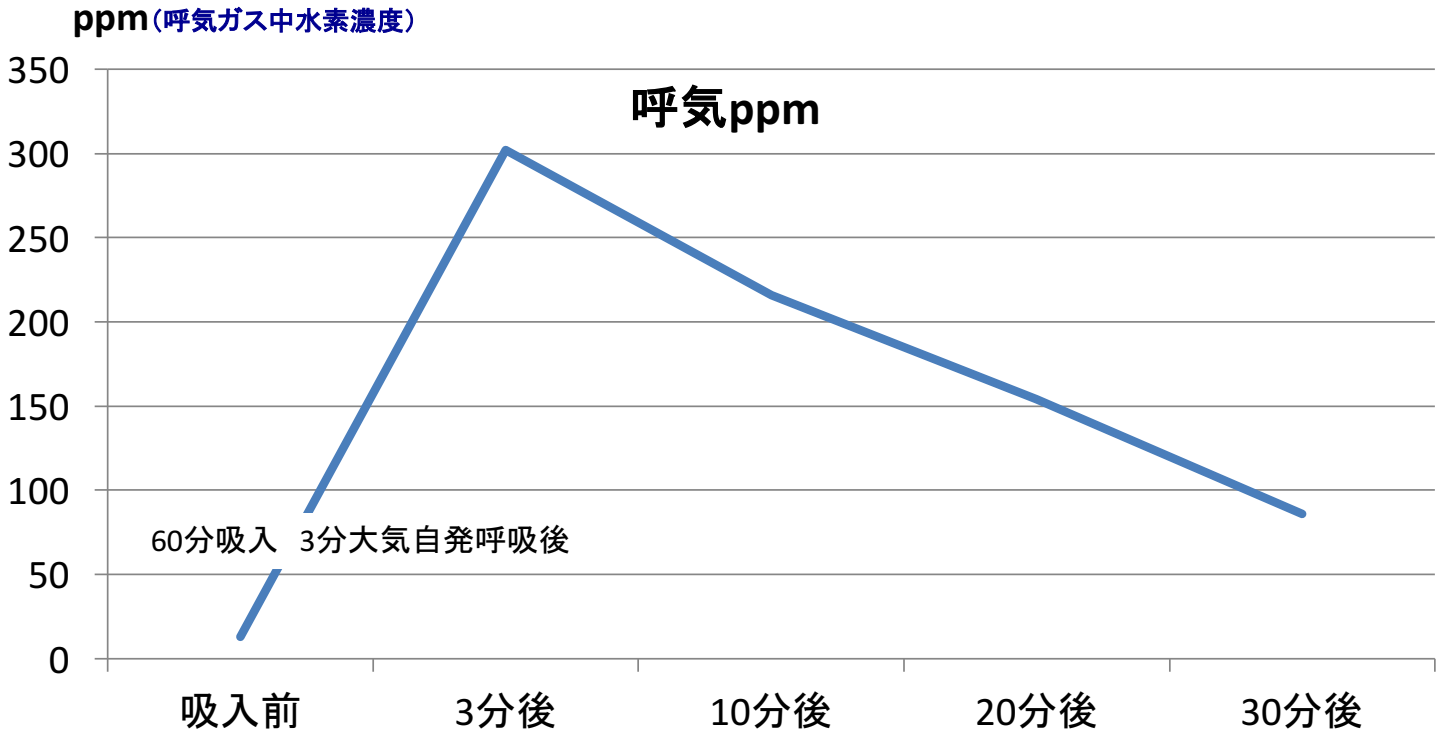


水素ガス（**物質**）
↓
↓
↓
水素分子（**分子**）

物質である水素ガスのファンデルワールス力結合を切断し
分子状水素として血中に取り込む必要がある≒ヘンリーの法則

研究段階の水素吸入について

吸入ガス成分　<発生　：　水素:60%　酸素:30%　水蒸気:10%> + 外気

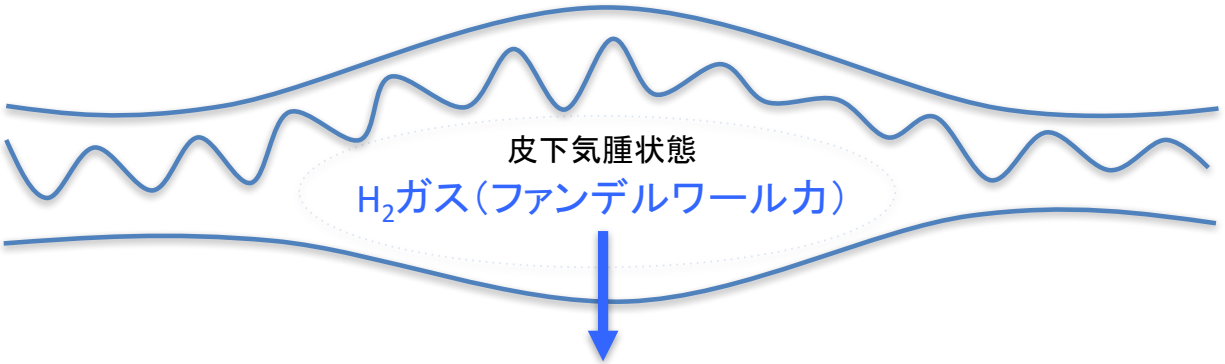


現段階で血中からの遊離か死腔の残存水素なのかは不明

ガス注射

皮内/皮下への水素ガス注射

分子間力が存在するため、すぐに吸収されるわけではない



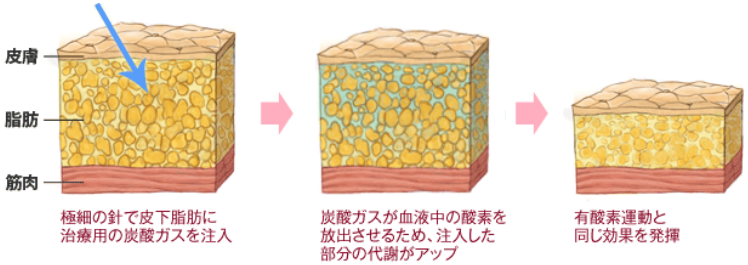
体液/間質液への拡散（分子状水素）:移行部：1.6ppm? ▶ 作用

血中/リンパ液中へ移行:移行部：1.6ppm ⟶ 作用

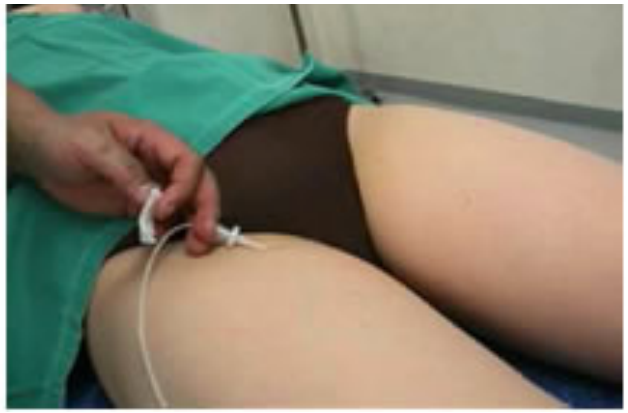
他のガス注射治療

カーボメッド（CARBOMED™）

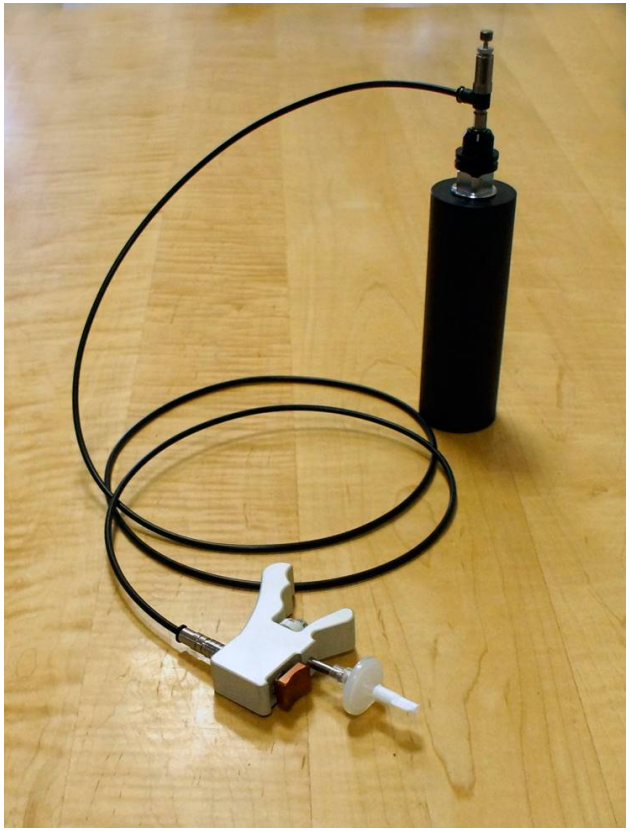
皮下組織（脂肪層）に炭酸ガスを注入
・セルライトの破壊
・代謝促進
による痩身目的の治療に使用



takasu.co.jpより



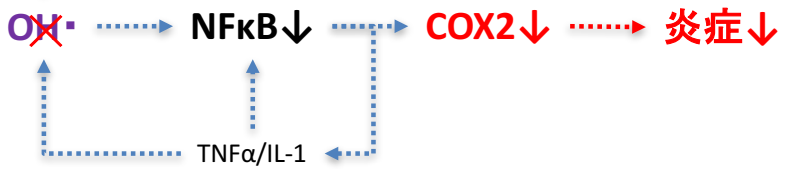
水素（ガス）注射



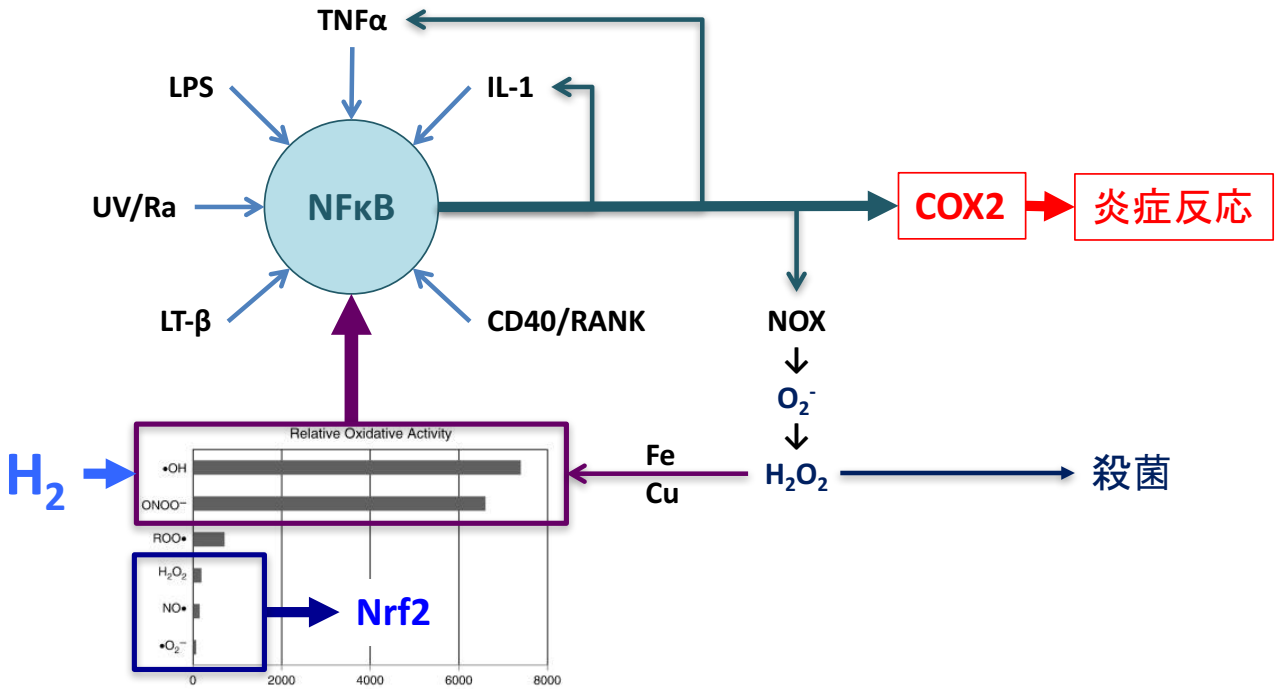
無菌H_2ガス

ボンベ内ガス濃度	: >99.999%
充填ガス濃度	: 99.9999%
湿度	: 0%
充填圧	: **0~100kPa**
投与量	: **Xml**

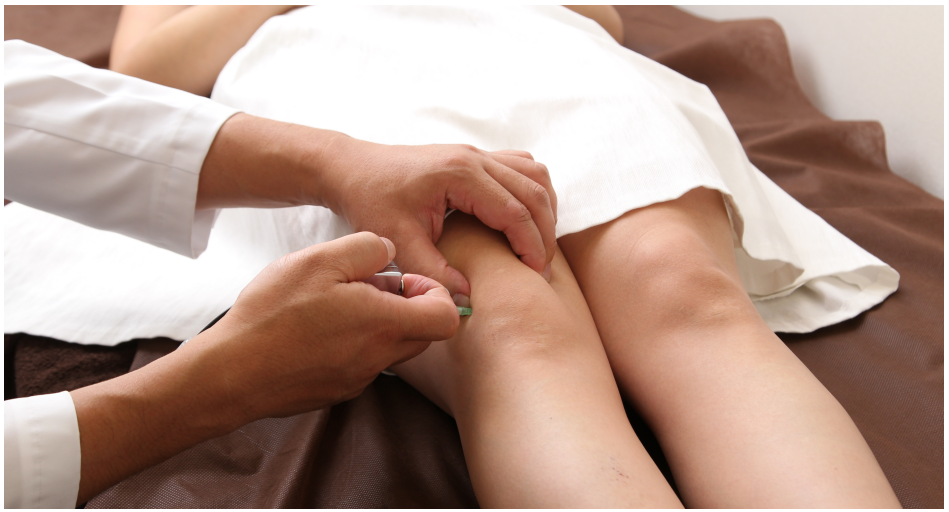
・充填圧による細胞/組織の損傷
・部位別の投与量



炎症と活性酸素


TNFα
LPS
IL-1
UV/Ra
NFκB
COX2
炎症反応
LT-β
CD40/RANK
NOX
O_2^-
H_2
Relative Oxidative Activity
•OH
ONOO⁻
ROO•
H_2O_2
NO•
$•O_2^-$
0
2000
4000
6000
8000
Fe
Cu
H_2O_2
殺菌
Nrf2

関節内注射



注入スピードが重要！
急激だと注入圧による疼痛

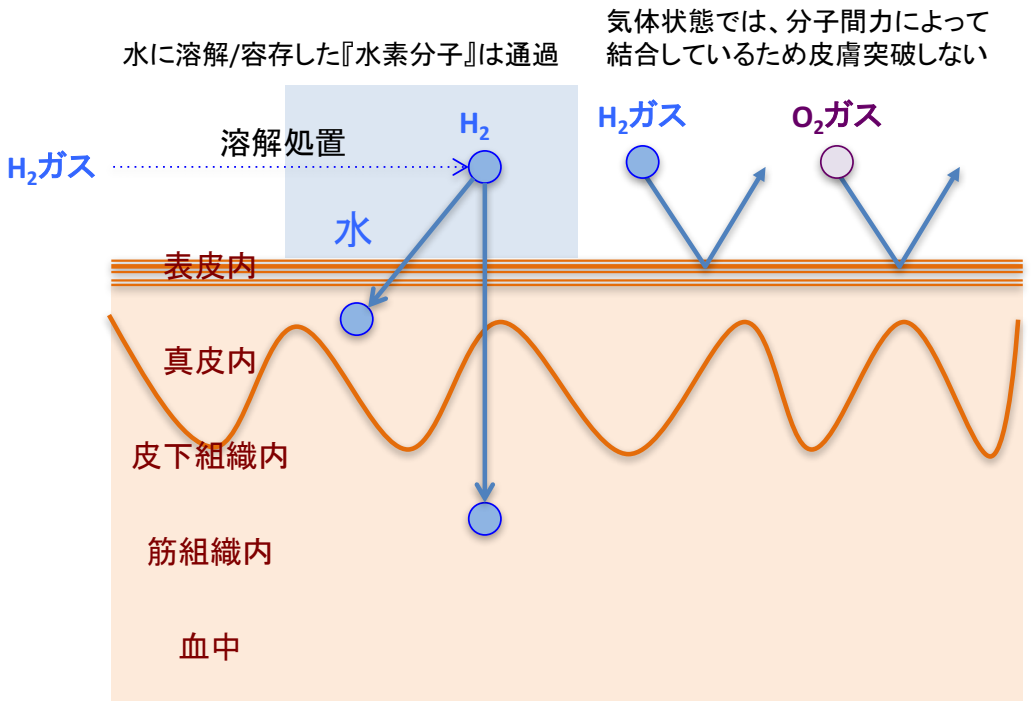
疼痛緩和の仮説

関節腔内への無菌100%水素ガス投与
（関節内閉鎖空間への投与）
↓
関節液/滑液への溶解
関節包への浸潤
↓
炎症軽減/疼痛緩和

経皮吸収剤

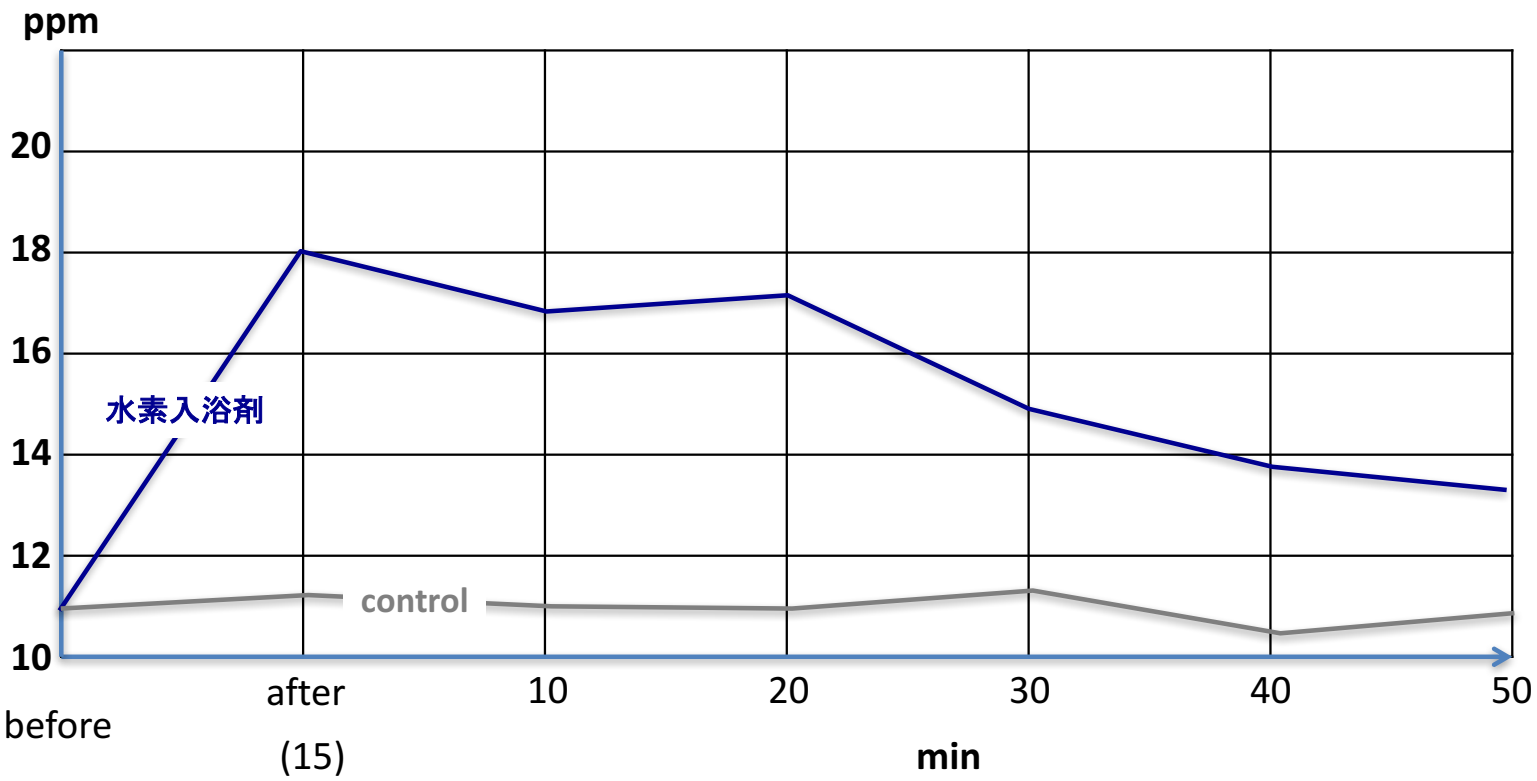
入浴剤/外用薬

経皮吸収
外用/入浴剤


水に溶解/容存した『水素分子』は通過
気体状態では、分子間力によって
結合しているため皮膚突破しない
H_2ガス
溶解処置
H_2
H_2ガス
O_2ガス
水
表皮内
真皮内
皮下組織内
筋組織内
血中

入浴による体内水素ガス動態

入浴による呼気ガス中水素濃度変化



医療法人社団医献会　辻クリニック

今後の課題

1:投与方法と投与量

- 腸内細菌水素ガス量から考えると、さらに高用量？
- →慎重に増量を検討中

2:Drug Delivery（拡散機序など）

- 素早い拡散スピードのコントロール法は？
- 脂肪層への拡散は？

3:患部（目的部位）の濃度

- 抗炎症に必要な用量は？
- 抗AGEに必要な用量は？

4:点滴/注射液における水素ナノバブルの作用

- ナノバブルの作用とは？
- 他のナノバブル（酸素ナノバブル/オゾンナノバブル）との違いは？

thank you !